

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
May 10, 2017**

Table of Contents

Helpful Hints/Reference Document	2
External Criteria	
Antihistamines (First Generation).....	4
Estrogens.....	5
Antidiabetic Agents	6
Prenatal Vitamins.....	7
Agenda	8
Pharmacotherapy Class Reviews and Re-Reviews	
Pharmacotherapy Review of First Generation Antihistamines.....	9
Pharmacotherapy Review of Estrogens	77
Pharmacotherapy Review of Alpha-Glucosidase Inhibitors.....	180
Pharmacotherapy Review of Amylinomimetics	232
Pharmacotherapy Review of Biguanides	270
Pharmacotherapy Review of Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	394
Pharmacotherapy Review of Incretin Mimetics	500
Pharmacotherapy Review of Insulins	598
Pharmacotherapy Review of Meglitinides.....	758
Pharmacotherapy Review of Sodium-glucose Cotransport 1 Inhibitors.....	814
Pharmacotherapy Review of Sodium-glucose Cotransport 2 Inhibitors.....	815
Pharmacotherapy Review of Sulfonylureas.....	868
Pharmacotherapy Review of Thiazolidinediones	993
Pharmacotherapy Review of Antidiabetic Agents, Miscellaneous.....	1112
Pharmacotherapy Review of Multivitamin Preparations: Prenatal Vitamins	1121
Pharmacotherapy Review of Immunomodulatory Agents used to treat Multiple Sclerosis.....	1148
Pharmacotherapy New Drug Review	
Pharmacotherapy Review of Dyanavel [®] XR	1240

Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document
P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Preferred with Clinical Criteria: Listed on the Agency's Preferred Drug Lists but will require a prior authorization. Clinical criteria must be met in order to be approved. For a non-preferred product to be approved, failure with a designated number of preferred agents and clinical criteria must be met.

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
 - DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
 - Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
 - Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
 - Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are in Non-preferred status or if they required PA prior to the PDL

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

- Maximum Unit Limitations
- Early Refill
- Brand Limit Switchover
- Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) or ICD-9 code(s) may be used. Use of ICD-9 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications provided through a government or state sponsored drug assistance program for uninsured patients may be counted toward the stable therapy requirement. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Antihistamines (First Generation)

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Antihistamines are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Estrogens

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred estrogens in this class, either generic, OTC or brand, within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Estrogens are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Antidiabetic Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred antidiabetic agents, either generic, OTC or brand, within the past 12 months, or have a documented allergy or contraindication to all preferred agents in this class.
- If the request is for Avandia[®], Avandamet[®], or Avandaryl[®], the patient must also have failed a 30-day treatment trial with at least two prescribed and preferred antidiabetic agents (of which one is Actos[®]), either generic, OTC or brand, within the past 6 months.
- If the request is for Symlin[®], the patient must also be on insulin therapy and have a hemoglobin A1c greater than 7% despite more than 90 days of insulin therapy.
- If the request is for Korlym[®], the patient must be ≥18 years of age with endogenous Cushing's syndrome with type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

Stable Therapy

- Approval may be given for those who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Antidiabetic agents, excluding Symlin[®], are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Prenatal Vitamins

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Not Applicable

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

May 10, 2017
9:00 a.m. – 12:00 noon

1. Opening remarks.....Chair
2. Approval of February 8, 2017 P&T Committee Meeting minutes.....Chair
3. Pharmacy program update.....Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives
(prior to each respective class review)
5. Pharmacotherapy class re-reviews.....University of Massachusetts Medical School
Clinical Pharmacy Services
 - First Generation Antihistamines
 - Ethanolamine Derivatives-AHFS 040404
 - Ethylenediamine Derivatives-AHFS 040408
 - Propylamine Derivatives-AHFS 040420
 - Estrogens-AHFS 681604
 - Alpha Glucosidase Inhibitors-AHFS 682002
 - Amylinomimetics-AHFS 682003
 - Biguanides-AHFS 682004
 - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors-AHFS 682005
 - Incretin Mimetics-AHFS 682006
 - Insulins-AHFS 682008
 - Meglitinide-AHFS 682016
 - Sodium-glucose Cotransport 1 Inhibitors- AHFS 682017
 - Sodium-glucose Cotransport 2 Inhibitors- AHFS 682018
 - Sulfonylureas-AHFS 682020
 - Thiazolidinediones-AHFS 682028
 - Antidiabetic Agents, Miscellaneous-AHFS 682092
 - Multivitamin Preparations: Prenatal Vitamins-AHFS 882800
 - Immunomodulatory Agents used to treat Multiple Sclerosis-AHFS 922000
6. New drug review..... University of Massachusetts Medical School
 - Dyanavel XR® (Amphetamines)-AHFS 282004
7. Results of voting announced.....Chair
8. New business
9. Next meeting dates:
 - August 9, 2017
 - November 8, 2017
10. Adjourn

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of First Generation Antihistamines
Ethanolamine Derivatives, AHFS Class 040404
Ethylenediamine Derivatives, AHFS Class 040408
Propylamine Derivatives, AHFS Class 040420
May 10, 2017**

I. Overview

The H₁-antihistamines are approved for the treatment of allergic and non-allergic conditions; however, they are primarily used for the management of allergic rhinitis, urticaria, and angioedema. Allergic rhinitis is a common disorder that is associated with significant morbidity, including lost school/work days, interference with activities of daily living, and a decrease in quality of life. Nasal symptoms include sneezing, itching, rhinorrhea, and congestion. Rhinitis may also be accompanied by symptoms involving the eyes, ears, and throat.¹ Urticaria is a common disorder characterized by pruritic, raised, erythematous plaques. Lesions may appear on any part of the body; however, they frequently appear on the trunk and extremities. As is seen with allergic rhinitis, intense itching may interfere with sleep, school/work productivity, and quality of life. Angioedema is characterized by swelling of deeper subcutaneous tissues, with less circumscribed lesions. It often involves the face, eyelids, lips, and tongue and may be life-threatening if laryngeal edema or tongue swelling obstructs the airway.^{2,3}

H₁-antihistamines reduce the physiologic effects elicited by histamine at the H₁-receptor; however, they do not prevent the release of histamine or bind to histamine that has already been released. They are classified as first generation and second generation agents. First generation antihistamines bind to both central and peripheral H₁-receptors, whereas second generation agents are more selective for peripheral H₁-receptors. As a result, the first generation antihistamines may cause sedation, performance impairment in school and driving, as well as anticholinergic effects.⁴

The first generation antihistamines include ethanolamine derivatives (carbinoxamine, clemastine, and diphenhydramine), ethylenediamine derivatives (no current agents), and propylamine derivatives (chlorpheniramine,). They are available as single entity agents, as well as in combination with other first generation antihistamines and oral decongestants.

The first generation antihistamines that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The eye, ear, nose, and throat anti-allergic agents (American Hospital Formulary Service 520200) were previously reviewed and are not included in this review. All of the first generation antihistamines are available in a generic formulation. Cough and cold products are an excludable/optional drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90). Brand cough and cold products are not covered by Alabama Medicaid; therefore, these products were not included in this review. The second generation antihistamines (acrivastine, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine) are not included on the mandatory preferred drug list. Brand products currently require prior authorization. Covered generics (unless otherwise specified) do not require prior authorization. Although the second generation antihistamines may be mentioned throughout this review, they are not being considered for preferred status at this time. This class was last reviewed in February 2015.

Table 1. First Generation Antihistamines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ethanolamine Derivatives			
Carbinoxamine	solution, tablet	Arbinoxa ^{®*} , Karbinal ER [®]	carbinoxamine
Clemastine	syrup, tablet	N/A	clemastine
Diphenhydramine	elixir, injection	N/A	diphenhydramine
Propylamine Derivatives			
Phenylephrine and chlorpheniramine	drops	N/A	phenylephrine and chlorpheniramine

*Generic is available in at least one dosage form or strength
N/A=Not available; PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the first generation antihistamines are summarized in Table 2.

Table 2. Treatment Guidelines Using the First Generation Antihistamines

Clinical Guideline	Recommendation(s)
<p>American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: The Diagnosis and Management of Anaphylaxis: A Practice Parameter Update (2015)⁵</p>	<ul style="list-style-type: none"> • Any patient who has experienced an episode of anaphylaxis should be evaluated to determine the causative agent. When the cause is not readily identified, the patient should be referred to an allergist or immunologist to conduct this evaluation. • Any patient who has experienced anaphylaxis when the cause is not completely avoidable or cannot be determined should be supplied with an auto-injectable epinephrine and should be instructed in the use of this device and told to keep their auto-injectable epinephrine with them at all times. The patient should be taught to recognize the signs and symptoms of anaphylaxis and when to administer the injection and be given an anaphylaxis action plan. Because anaphylactic episodes might require more than one dose of epinephrine, all patients should carry two auto-injectable epinephrines. • The patient should be instructed to wear and carry identification denoting the patient's condition. • Individual risk factors should be taken into consideration. These include age, activity, occupation, hobbies, residential conditions, and access to medical care. It is important to consider the patient's level of anxiety, and attempts should be made to have patients gain confidence in their ability to treat any future event. • Pharmacologic prophylaxis such as glucocorticosteroids and antihistamines can be used in select situations such as in the prevention of anaphylaxis to drugs or biologic agents (e.g., radiocontrast material) or to prevent recurrent episodes of idiopathic anaphylaxis. • Any patient subject to episodes of anaphylaxis should be counseled regarding the use of certain medications that could worsen any future event or complicate therapy (e.g., β-adrenergic blockers). • The appropriate treatment of an acute event that might occur in a medical office requires planning and preparation. Plan for an appropriate office response to anaphylaxis by (1) educating staff and patients; (2) preparing an anaphylaxis emergency cart; and (3) developing an office action plan for anaphylaxis management to maintain proficiency. • At the onset of anaphylaxis, (1) administer epinephrine intramuscularly in the mid-outer thigh; (2) remove the inciting allergen, if possible (e.g., stop an infusion); (3) quickly assess airway, breathing, circulation, and mentation, and summon appropriate assistance from staff members; and (4) start, if needed, cardiopulmonary resuscitation and summon emergency medical services. • Recognize that more than one epinephrine injection might be necessary in some patients. • Intravenous fluid replacement with normal saline is indicated for patients with circulatory collapse and for patients who do not respond to intramuscular epinephrine. Hypotension of any degree should prompt the administration of intravenous fluid. • For respiratory symptoms not responding to epinephrine, nebulized β2-agonists such as albuterol should be administered. • In patients who are receiving β-adrenergic blocking agents, glucagon should be administered if there is a failure to respond to epinephrine. • H1 and H2 antihistamines or corticosteroids can be given as adjunctive therapy after the administration of epinephrine but are not indicated as initial treatment for anaphylaxis in place of epinephrine. Consider these agents as optional therapy. • On release from treatment, all patients should be prescribed an auto-injectable epinephrine, given an anaphylaxis action plan, and educated in the symptoms that

Clinical Guideline	Recommendation(s)
	<p>might indicate another reaction. Foods are the most common cause of anaphylaxis, followed by drugs.</p> <ul style="list-style-type: none"> As with all other causes of anaphylaxis, patients who have experienced an episode of anaphylaxis to foods should be supplied with auto-injectable epinephrine, instructed in their use, taught the signs and symptoms of anaphylaxis, and given an anaphylaxis action plan. Medications rival food for the most common cause of anaphylaxis. The most common classes of drugs producing anaphylaxis are (1) antibiotics, especially beta-lactam antibiotics, and (2) nonsteroidal anti-inflammatory drugs (NSAIDs).
<p>American Academy of Dermatology Clinical Guidelines Task Force: Guidelines of Care for the Management of Atopic Dermatitis (2014)⁶⁻⁷</p>	<p><u>Topical corticosteroids</u></p> <ul style="list-style-type: none"> Topical corticosteroids (TCs) are used in the management of atopic dermatitis in both adults and children and are the mainstay of anti-inflammatory therapy. TCs are typically introduced into the treatment regimen after failure of lesions to respond to good skin care and regular use of moisturizers alone. TCs are used for both active inflammatory disease and for prevention of relapses. There are no data to support one or a few specific agents as being more efficacious than others. Most studies involve twice daily application. This is the most common clinical practice and also the generally recommended frequency. However, there is evidence to support that once daily application of some potent corticosteroids may be as effective as twice daily application. Some newer formulations also use once daily application. <p><u>Topical calcineurin inhibitors</u></p> <ul style="list-style-type: none"> The two available topical calcineurin inhibitors (TCIs), tacrolimus ointment and pimecrolimus cream, have been shown to be more effective than vehicle in short-term and long-term studies in adults and children with active disease. Tacrolimus is approved for moderate to severe disease, where pimecrolimus is indicated for mild to moderate atopic dermatitis, and six-week comparative studies support a greater effect for tacrolimus for all severities. Twice daily application of the tacrolimus ointments and pimecrolimus cream are significantly more effective at decreasing signs of inflammation, affected body surface area, and associated pruritus of lesional areas on the head/neck and non-head/neck locations than vehicle or once-daily application in adults, children, and infants. Proactive, intermittent application of TCI two to three times weekly to recurrent sites of disease has also been shown to be effective in reducing relapses. <p><u>Topical antimicrobials and antiseptics</u></p> <ul style="list-style-type: none"> Patients with atopic dermatitis are commonly colonized with <i>Staphylococcus aureus</i>. No clear benefit for topical antibiotics/antiseptics, antibacterial soaps, or antibacterial bath additives has been established. Thus, topical antimicrobial preparations are not generally recommended in the treatment of atopic dermatitis. <p><u>Topical antihistamines</u></p> <ul style="list-style-type: none"> Topical antihistamines have been tried for the treatment of atopic dermatitis but have demonstrated little utility and are not recommended. <p><u>Systemic agents</u></p> <ul style="list-style-type: none"> Systemic agents are recommended in the subset of atopic dermatitis patients in whom optimized topical regimens and/or phototherapy do not adequately control the disease, or when quality of life is substantially impacted. All immunomodulatory agents should be adjusted to the minimal effective dose once response is attained and sustained.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Adjunctive therapies should be continued to use the lowest dose and duration of systemic agent possible. • Insufficient data exist to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunomodulating medication. • Treatment decisions should be based on each individual patient’s atopic dermatitis status (current and historical), comorbidities, and preferences. • Cyclosporine is effective and recommended as a treatment option for patients with atopic dermatitis refractory to conventional topical treatment. • Azathioprine is recommended as a systemic agent for the treatment of refractory atopic dermatitis. • Methotrexate is recommended as a systemic agent for the treatment of refractory atopic dermatitis. Folate supplementation is recommended during treatment with methotrexate. • Mycophenolate mofetil may be considered as an alternative, variably effective therapy for refractory atopic dermatitis. • Interferon gamma is moderately and variably effective and may be considered as an alternative therapy for refractory atopic dermatitis in adults and children who have not responded to, or have contraindications to the use of, other systemic therapies or phototherapy. • Systemic steroids should be avoided if possible for the treatment of atopic dermatitis. Their use should be exclusively reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapy. • The use of systemic antibiotics in the treatment of noninfected atopic dermatitis is not recommended. Systemic antibiotics are appropriate and can be recommended for use in patients with clinical evidence of bacterial infections in addition to standard and appropriate treatments for atopic dermatitis disease itself (which may include the concurrent use of topical corticosteroids). Systemic antiviral agents should be used for the treatment of eczema herpeticum. • There is insufficient evidence to recommend the general use of oral antihistamines as part of the treatment of atopic dermatitis. Short-term, intermittent use of sedating antihistamines may be beneficial in the setting of sleep loss secondary to itch, but should not be substituted for management of atopic dermatitis with topical therapies. Nonsedating antihistamines are not recommended as a routine treatment for atopic dermatitis in the absence of urticaria or other atopic conditions such as rhinoconjunctivitis.
<p>American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: Disease Management of Atopic Dermatitis: An Updated Practice Parameter (2013)⁸</p>	<p><u>General considerations</u></p> <ul style="list-style-type: none"> • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness. The clinician should establish treatment goals with the patient, which may include reduction in number and severity of flares and increase in disease-free periods. • Clinicians should use a systematic, multipronged approach that includes skin hydration, topical anti-inflammatory medications, antipruritic therapy, antibacterial measures, and elimination of exacerbating factors. <p><u>Skin hydration</u></p> <ul style="list-style-type: none"> • Atopic dermatitis is characterized by reduced skin barrier function, which leads to enhanced water loss and dry skin; therefore, hydration with warm soaking baths for at least 10 minutes followed by application of a moisturizer is recommended as first-line therapy. <p><u>Topical corticosteroids</u></p> <ul style="list-style-type: none"> • If atopic dermatitis is not controlled by moisturizers alone, a topical corticosteroid is recommended.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate and high-potency corticosteroids should be used for the treatment of clinical exacerbation over short periods of time. Clinicians should not prescribe potent fluorinated corticosteroids for use on the face, eyelids, genitalia, and intertriginous areas or in young infants. Ultrahigh-potency corticosteroids are recommended only for very short periods (1 to 2 weeks) and in nonfacial non-skinfold areas. • When prescribing topical steroids, clinicians should remember that the degree of corticosteroid absorption through the skin and hence the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. <p><u>Topical calcineurin inhibitors</u></p> <ul style="list-style-type: none"> • Clinicians can consider the use of tacrolimus ointment, which has been shown to be effective and safe in both adults and children older than two years for the treatment of atopic dermatitis, with most patients experiencing a reduction of pruritus within three days of initiating therapy. Tacrolimus ointment, which, unlike topical steroids, does not cause atrophy for eczema on the face, eyelid, and skin folds, is an option for patients unresponsive to low-potency topical steroids. Topical tacrolimus can cause transient localized burning and itching during the first week of therapy. This might limit its usefulness in certain patients. Once a flare is controlled, the clinician might consider prescribing tacrolimus ointment twice daily, twice weekly to eczema-prone areas to prevent future flares. • Clinicians should consider the use of topical pimecrolimus cream, which is a calcineurin inhibitor that safely decreases the number of flares, reduces the need for corticosteroids, does not cause skin atrophy, and controls pruritus. <p><u>Tar preparations</u></p> <ul style="list-style-type: none"> • Although tar preparations are widely used, there are no randomized controlled studies that have demonstrated their efficacy. Tar should not be recommended for acutely inflamed skin because this might result in additional skin irritation. <p><u>Antihistamines</u></p> <ul style="list-style-type: none"> • Some patients may benefit from the use of antihistamines for the relief of pruritus. Treatment with topical antihistamines is not recommended because of potential cutaneous sensitization. <p><u>Vitamin D</u></p> <ul style="list-style-type: none"> • Patient may benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. <p><u>Dilute bleach baths</u></p> <ul style="list-style-type: none"> • Consider the addition of dilute bleach baths twice weekly to reduce the severity of atopic dermatitis, especially in patients with recurrent skin infections. <p><u>Microbes</u></p> <ul style="list-style-type: none"> • Skin infections with <i>Staphylococcus aureus</i> are a recurrent problem in patients with atopic dermatitis, and patients with moderate-to-severe dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic should only be prescribed for patients who are clinically infected with <i>Staphylococcus aureus</i>. In areas with high levels of methicillin-resistant <i>Staphylococcus aureus</i>, the clinician might want to obtain a skin culture and initiate treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim while awaiting culture results. • Atopic dermatitis can be complicated by recurrent viral skin infections, such as

Clinical Guideline	Recommendation(s)
	<p>herpes simplex, warts, and molluscum contagiosum. Disseminated herpes simplex or eczema herpeticum should promptly be treated with systemic antiviral agents.</p> <ul style="list-style-type: none"> • Atopic dermatitis patients and their household should not be immunized with the smallpox vaccine because they can have a severe, widespread, potentially fatal cutaneous infection called eczema vaccinatum, which is similar in appearance to eczema herpeticum. • Consider fungal infections that can contribute to exacerbations. The diagnosis of dermatophytes can be made by using KOH preparation or culture. <i>Malassezia</i> species, which is a particular problem in young adults with refractory head and neck eczema, can be diagnosed clinically or with a KOH preparation. Specific IgE to <i>Malassezia</i> species might also be obtained.
<p>American Academy of Ophthalmology Preferred Practice Pattern Guidelines: Conjunctivitis (2013)⁹</p>	<p><u>Seasonal allergic conjunctivitis</u></p> <ul style="list-style-type: none"> • Mild allergic conjunctivitis can be treated with an over-the-counter antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H₁- receptor antagonists. • Mast-cell stabilizers can be utilized if the condition is recurrent or persistent. • Combination antihistamine and mast-cell stabilizer medications can be utilized for either acute or chronic disease. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of a low-potency topical corticosteroid can be added to the regimen. • A nonsteroidal anti-inflammatory agent (ketorolac) has been Food and Drug Administration (FDA)-approved for the treatment of allergic conjunctivitis. • Additional measures include the use of artificial tears, cool compresses, oral antihistamines, and allergen avoidance. Frequent clothes washing and bathing/showering before bedtime may also be helpful. • Use of topical mast-cell stabilizers can also be helpful in alleviating symptoms of allergic rhinitis, and intranasal corticosteroids are not effective for the treatment of seasonal allergic conjunctivitis. <p><u>Vernal/atopic conjunctivitis</u></p> <ul style="list-style-type: none"> • General treatment measures include minimizing exposure to allergens or irritants, and using cool compresses and ocular lubricants. • Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort. • Topical corticosteroids are usually necessary to control severe signs and symptoms during acute exacerbations. • Topical cyclosporine (2.0%) is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis. • For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, systemic immunosuppression may be warranted rarely. • In patients two years of age and older, eyelids can be treated with pimecrolimus cream (1.0%) or tacrolimus ointment applied to the affected eyelid skin. Both agents are rarely associated with development of skin cancer or lymphoma.
<p>American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: The Diagnosis and Management of</p>	<p><u>Pharmacologic therapy</u></p> <ul style="list-style-type: none"> • The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age. <p><u>Oral antihistamines</u></p> <ul style="list-style-type: none"> • First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. • First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of first-generation antihistamines has been associated with increased automobile

Clinical Guideline	Recommendation(s)
<p>Rhinitis: An Updated Practice Parameter (2008)¹</p>	<p>and occupational accidents.</p> <ul style="list-style-type: none"> • Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime. • The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines. • The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied. • Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. • Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. • Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines. • With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • No single second-generation antihistamine has been conclusively shown to have greater efficacy. <p><u>Intranasal antihistamines</u></p> <ul style="list-style-type: none"> • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines have been associated with sedation and can inhibit skin test reactions due to systemic absorption. • Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. • Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. <p><u>Oral decongestants</u></p> <ul style="list-style-type: none"> • Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations. • The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone. • Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine. • Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established. • Elevation of blood pressure after taking an oral decongestant is rarely seen in

Clinical Guideline	Recommendation(s)
	<p>normotensive patients and only occasionally in patients with controlled hypertension.</p> <ul style="list-style-type: none"> • Concomitant use of caffeine and stimulants may be associated with an increase in adverse events. • Oral decongestants should be used with caution in older adults and young children, and in patients of any age with a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. • Oral decongestants are usually well tolerated in children over six years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age. <p><u>Topical decongestants</u></p> <ul style="list-style-type: none"> • Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa. <p><u>Intranasal corticosteroids</u></p> <ul style="list-style-type: none"> • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. • Intranasal corticosteroids have been shown to be more effective than the combined use of an antihistamine and leukotriene antagonist in the treatment of seasonal allergic rhinitis in most studies. • The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported. <p><u>Oral corticosteroids</u></p> <ul style="list-style-type: none"> • A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. • Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. <p><u>Intranasal cromolyn</u></p> <ul style="list-style-type: none"> • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Intranasal cromolyn is less effective than corticosteroids in most patients and has not been adequately studied in comparison with leukotriene antagonists or antihistamines. <p><u>Intranasal anticholinergics</u></p> <ul style="list-style-type: none"> • Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. • Dryness of the nasal membranes may occur with intranasal anticholinergics. • The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events.

Clinical Guideline	Recommendation(s)
	<p><u>Oral antileukotriene agents</u></p> <ul style="list-style-type: none"> Oral antileukotriene agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. <p><u>Omalizumab</u></p> <ul style="list-style-type: none"> Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma. <p><u>Nasal saline</u></p> <ul style="list-style-type: none"> Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy. <p><u>Over-the-counter cough and cold medications for young children</u></p> <ul style="list-style-type: none"> The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years. Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age.
<p>Institute for Clinical Systems Improvement: Diagnosis and Treatment of Respiratory Illness in Children and Adults (2013)¹⁰</p>	<p><u>Strep pharyngitis</u></p> <ul style="list-style-type: none"> Penicillin is the drug of choice for treatment of culture positive cases of group A beta streptococcal pharyngitis. In children and patients unable to swallow pills, amoxicillin is an acceptable alternative due to the poor palatability of the penicillin suspension. In penicillin-allergic patients, options include cephalosporins (for some types of allergies), macrolides, and clindamycin. Consider reevaluating patient for carrier status. Although macrolides may be an acceptable alternative, clinicians should check their local resistance patterns. Alternative medication recommendations include macrolides, cephalexin, clindamycin, amoxicillin-clavulanate, and rocephin. <p><u>Non-infectious rhinitis</u></p> <ul style="list-style-type: none"> With the exception of systemic steroids, intranasal corticosteroids are the most effective single agents for controlling allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. Systemic corticosteroid use should be reserved for refractory or severe cases only and given as a short burst. Injectable corticosteroids are generally not recommended as they are invasive and tend to have a longer course of action than typical courses of corticosteroids. Antihistamines are effective at controlling all symptoms associated with allergic rhinitis, with the exception of nasal congestion. They are less than intranasal corticosteroids, but can be used either on a daily basis or on an as-needed basis. Second-generation antihistamines are less sedating than first-generation antihistamines, and cause less central nervous system impairment. Adverse events commonly associated with first-generation antihistamines include somnolence, decreased alertness, and anticholinergic effects. These agents may cause central nervous system impairment and impair driving performance. Oral decongestants can reduce nasal congestion but can result in side effects such as irritability, insomnia, and palpitations. Topical decongestants are used for short-term or intermittent/episodic therapy. Routine daily use is not recommended because of the risk for the development of rhinitis medicamentosa. Both oral and topical decongestants should be used with caution in older adults, children under the age of six, and patients of any age who have a history of the following: arrhythmia, angina, cerebrovascular disease, high blood pressure, bladder neck obstruction, glaucoma, or hyperthyroidism. Cromolyn is less effective than intranasal corticosteroids, and is most effective

Clinical Guideline	Recommendation(s)
	<p>when used regularly prior to the onset of allergic symptoms. Cromolyn is a good alternative for patients who are not candidates for corticosteroids.</p> <ul style="list-style-type: none"> • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in patients with allergic and non-allergic rhinitis. They have no effect on congestion, sneezing, or itching. • Montelukast is a leukotriene receptor antagonist that is as effective as loratadine and less effective than nasal steroids. It is generally well tolerated and may be considered as a third-line option to add after the failure of a nasal corticosteroid and an oral antihistamine. • Ophthalmic preparations contain antihistamines, decongestants, corticosteroids, combination antihistamines/decongestants, corticosteroids, or mast cell stabilizers. Topical antihistamines can be used as needed for acute symptomatic relief and prophylaxis of allergic rhinitis with minimal systemic side effects. <p><u>Non-allergic rhinitis</u></p> <ul style="list-style-type: none"> • Treatment of symptomatic nasal obstruction due to non-allergic rhinitis includes the use of azelastine nasal spray, intranasal corticosteroids, intranasal cromolyn, oral decongestants, nasal strips, and topical antihistamines. • Intranasal corticosteroids can be used to treat chronic nasal congestion secondary to non-allergic rhinitis. Intranasal corticosteroids have a relatively long onset of action (up to four weeks) and are therefore better suited to patients with chronic symptoms. • Intranasal cromolyn may improve sneezing and congestion scores, and it can be safely used in children two years of age and older. • Some patients find oral decongestants helpful at relieving symptomatic nasal obstruction secondary to non-allergic rhinitis. Oral decongestants have a relatively rapid onset of action and therefore are particularly useful for sporadic symptoms. Patients using oral decongestants should be monitored for hypertension. • Nasal strips may be effective for patients with nocturnal symptoms. They are more effective for patients with narrow noses or with anterior septal deviations. Daytime use of nasal strips is not usually practical. • Topical antihistamines have been shown to be effective in controlling rhinorrhea associated with non-allergic rhinitis. • Conservative treatment of symptomatic non-purulent chronic posterior nasal drainage includes increased water intake, decreased caffeine and alcohol intake, nasal saline irrigation, use of petroleum jelly or antibiotic ointment for nasal crusting, and the addition of humidity in bedroom, if significantly less than 50%. In addition, it should be determined if the patient is using any medications that may cause oral or nasal dryness. • Medical treatment of symptomatic non-purulent chronic posterior nasal drainage includes intranasal corticosteroids. • Treatment of symptomatic bilateral chronic anterior rhinorrhea due to non-allergic rhinitis includes avoidance of triggers, intranasal corticosteroids, intranasal ipratropium bromide, and nasal saline. <p><u>Bacterial sinusitis</u></p> <ul style="list-style-type: none"> • Intranasal corticosteroids may be rational but is an unproved adjunctive therapy for acute sinusitis. This therapy may be appropriate for selected cases of recurrent sinusitis, especially in the presence of an allergy or inflammation etiology. • Antibiotics should be reserved for those patients who failed decongestant therapy, those we present with symptoms and signs of a more severe illness, and those who have complications of acute sinusitis.
Global Allergy and	<u>Pharmacologic treatment of allergic rhinitis</u>

Clinical Guideline	Recommendation(s)
<p>Asthma European Network: Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)¹¹</p>	<ul style="list-style-type: none"> • New-generation oral H₁-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis. • New-generation oral H₁-antihistamines are recommended over old-generation oral H₁-antihistamines. • In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral H₁-antihistamines not be used to prevent wheezing or asthma. • Intranasal H₁-antihistamines are suggested in adults and children with seasonal allergic rhinitis. • New-generation oral H₁-antihistamines are suggested over intranasal H₁-antihistamines in adults with seasonal allergic rhinitis and in adults with persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis. • Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis. • Oral H₁-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis. • Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis. • For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are suggested over oral H₁-antihistamines in adults and children. • Intranasal glucocorticosteroids are recommended over intranasal H₁-antihistamines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis. • For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested. • Intramuscular glucocorticosteroids are not recommended for allergic rhinitis. • Intranasal chromones are suggested for allergic rhinitis, and intranasal H₁-antihistamines are suggested over intranasal chromones. • Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis. • A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children. • It is suggested that regular use of oral decongestants, either alone or in combination with an oral H₁-antihistamine, not occur in patients with allergic rhinitis. • Intraocular H₁-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis.
<p>International Primary Care Respiratory Group Guidelines: Management of Allergic Rhinitis (2006)¹²</p>	<p><u>Mild intermittent allergic rhinitis</u></p> <ul style="list-style-type: none"> • Recommended therapy: <ul style="list-style-type: none"> ○ Oral H₁-blocker. ○ Intranasal H₁-blocker. ○ Decongestant. AND/OR <ul style="list-style-type: none"> ○ Intranasal saline. • Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe intermittent allergic rhinitis treatment options).

Clinical Guideline	Recommendation(s)
	<p><u>Moderate/severe intermittent allergic rhinitis</u></p> <ul style="list-style-type: none"> • Recommended therapy: <ul style="list-style-type: none"> ○ Oral H₁-blocker. ○ Intranasal H₁-blocker. AND/OR <ul style="list-style-type: none"> ○ Decongestant. ○ Intranasal saline. ○ Intranasal glucocorticosteroid. ○ Mast cell stabilizer. ○ Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis and compliance, query infections and other causes, then consider trial of different treatment option or specialist referral. <p><u>Mild persistent allergic rhinitis</u></p> <ul style="list-style-type: none"> • Recommended therapy: <ul style="list-style-type: none"> ○ Oral H₁-blocker. ○ Intranasal H₁-blocker. AND/OR <ul style="list-style-type: none"> ○ Decongestant. ○ Intranasal glucocorticosteroid. ○ Intranasal saline. ○ Mast cell stabilizer. ○ Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe persistent allergic rhinitis treatment options). <p><u>Moderate/severe persistent allergic rhinitis</u></p> <ul style="list-style-type: none"> • Recommended therapy: <ul style="list-style-type: none"> ○ Intranasal glucocorticosteroid. ○ Decongestant. ○ Oral H₁-blocker. ○ Intranasal saline. ○ Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then choose one or more of the following options: <ul style="list-style-type: none"> ○ Increase nasal steroid dose, consider trial of different treatment option, or consider referral to specialist. ○ If sneeze/itch: add H₁-blocker. ○ If rhinorrhea: add ipratropium. ○ If blockage: add decongestant or short course of oral steroids. <p><u>General treatment considerations</u></p> <ul style="list-style-type: none"> • First generation H₁-antihistamines cause sedation and central nervous system impairment. These side effects may adversely affect cognition, learning and driving. These side effects may be potentiated by alcohol and other sedatives. Adverse events may not always be perceived by patients. • Second generation H₁-antihistamines are associated with less sedation and impairment than first generation antihistamines.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Intranasal and intraocular H₁-antihistamines are as effective as oral antihistamines at the site of their administration. • Intranasal glucocorticosteroids are the most effective class of medications available for the treatment of allergic and nonallergic rhinitis. Oral glucocorticosteroids are rarely needed to control severe symptoms of allergic rhinitis. • Mast cell stabilizers reduce symptoms of allergic rhinitis, but are generally less effective than other treatments and require frequent administration. Ocular mast cell stabilizers are effective and have a role in the treatment of allergic conjunctivitis. • Anticholinergic agents can reduce rhinorrhea, but have little effect on other symptoms of allergic rhinitis. • Antileukotriene agents are effective for the treatment of allergic rhinitis and asthma. They have been shown to be as effective as oral antihistamines, but have a greater effect on nasal obstruction. They may have an additive effect with antihistamines.
<p>American Academy of Otolaryngology–Head and Neck Surgery Foundation: Clinical Practice Guideline (update): Adult Sinusitis (2015)¹³</p>	<p>Symptomatic relief of viral rhinosinusitis</p> <ul style="list-style-type: none"> • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Topical or systemic decongestants may offer additional symptomatic relief. • Antihistamines have been used to treat viral rhinosinusitis due to their drying effect; however, no studies have been published that assess the impact of antihistamines specifically on viral rhinosinusitis outcomes. Adverse effects of antihistamines, especially first-generation H₁-antagonists, include drowsiness, behavioral changes, and impaired mucus transport in the nose and sinuses because of drying. <p>Symptomatic relief of acute bacterial rhinosinusitis</p> <ul style="list-style-type: none"> • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, saline irrigation, and topical nasal steroids. Use of interventions with questionable or unproven efficacy (antihistamines, systemic steroids) is discouraged. Commonly used interventions (decongestants, guaifenesin) with unknown effects on acute bacterial rhinosinusitis symptoms may be considered. • Adjunctive treatments for rhinosinusitis that may aid in symptomatic relief include analgesics, decongestants (α-adrenergic), corticosteroids, saline irrigation, and mucolytics. None of these products has been specifically approved by the Food and Drug Administration (FDA) for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. There are no studies that support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. • Antihistamines may be considered in patients with acute bacterial rhinosinusitis whose symptoms suggest a significant allergic component. <p>Watchful waiting for acute bacterial rhinosinusitis</p> <ul style="list-style-type: none"> • Observation without use of antibiotics is an option for selected adults with uncomplicated acute bacterial rhinosinusitis (regardless of severity). <p>Choice of antibiotic for acute bacterial rhinosinusitis</p> <ul style="list-style-type: none"> • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to 10 days for most adults.

Clinical Guideline	Recommendation(s)
	<p><u>Treatment failure for acute bacterial rhinosinusitis</u></p> <ul style="list-style-type: none"> • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
<p>American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)¹⁴</p>	<p><u>Acute bacterial rhinosinusitis</u></p> <ul style="list-style-type: none"> • Acute bacterial rhinosinusitis is defined as symptoms and signs for less than 12 weeks. The diagnosis of acute rhinosinusitis is based primarily on the clinical history, the physical examination, and possibly other ancillary evaluations, including endoscopy or radiographic imaging. In most instances the diagnosis is made presumptively, and treatment is initiated. • Patients with obvious acute bacterial rhinosinusitis should be carefully reviewed for any possible evidence of complicating factors, including the presence of facial swelling, erythema over an involved sinus, visual changes, abnormal extraocular movements, proptosis, periorbital inflammation, any suggestion of intracranial involvement, or central nervous system involvement manifested as abnormal neurologic signs. • Empiric treatment with an antibiotic approved by the FDA should be started once the diagnosis is made. Empiric therapy is administered for seven to 14 days. FDA-approved antibiotics include amoxicillin, amoxicillin-clavulanate, cefaclor, cefprozil, cefuroxime, cefdinir, cefixime, azithromycin, levofloxacin, trimethoprim-sulfamethoxazole, doxycycline, and clindamycin. Fluoroquinolones and doxycycline should be avoided in children. Nasal steroids may be of benefit, especially in allergic individuals. • A systematic review of antihistamines and decongestants in common colds found that there is insufficient evidence to suggest that antihistamines or decongestants are of benefit for the common cold. Antihistamines may slightly alleviate rhinorrhea and sneezing, but the overall benefit is minimal. Decongestants decrease congestion over six to 10 hours, but there is no evidence to suggest benefit for longer than 10 hours. • The following comfort measures might be helpful: adequate rest, adequate hydration, analgesics as needed, warm facial packs, steamy showers, and sleeping with the head of the bed elevated. Patients should be instructed to follow up if symptoms worsen (e.g., especially with headache or high fever) or if symptoms have not improved within three to five days of treatment. • For partial response, continue antibiotic treatment for another 10 to 14 days or consider a different antibiotic. • For poor response, which worsens after three to five days, consider broadening the microbial coverage provided by the antibiotic or switch to a different antimicrobial that covers resistant bacteria. • Rhinosinusitis that fails to improve after 21 to 28 days of initial antibiotic treatment might be caused by pathogens not adequately covered by prior antibiotics, nasal polyps, tumor, or noncompliance. <p><u>Chronic rhinosinusitis</u></p> <ul style="list-style-type: none"> • Clinicians should use systemic antibiotics for acute exacerbations of chronic rhinosinusitis. However, in some patients, this may not be necessary. • Consider a three- to six-week course of topical antibiotics for chronic rhinosinusitis. • Consider the use of systemic antibiotics plus a short course of oral steroids in the treatment of chronic rhinosinusitis. Greater benefit with antibiotics has been

Clinical Guideline	Recommendation(s)
	<p>reported in patients without nasal polyps then with nasal polyps.</p> <ul style="list-style-type: none"> • Consider a short course of oral steroids for the treatment of patients without nasal polyps. • Use short-term treatment with oral steroids in patients with nasal polyps because it decreases nasal polyp size and symptoms. • Use intranasal corticosteroid (INS; sprays and aerosols) for the treatment of patients with or without nasal polyps. • Use nasal saline irrigation as an adjunctive treatment for the therapy of chronic rhinosinusitis. • Consider antihistamines for treatment of symptoms associated with acute rhinosinusitis in patients with coexistent chronic rhinosinusitis. • Neither oral nor topical decongestants are beneficial for maintenance treatment of chronic rhinosinusitis.
<p>British Association of Dermatologists Therapy Guidelines and Audit Subcommittee: Guidelines for Evaluation and Management of Urticaria in Adults and Children (2007)²</p>	<p><u>Antihistamines</u></p> <ul style="list-style-type: none"> • Antihistamines are effective and safe for the treatment of urticaria; however, not all patients respond and some become worse. • All patients should be offered the choice of at least two nonsedating H₁-antihistamines because responses and tolerance vary between individuals. • It has become common practice to increase the dose above the manufacturer's licensed recommendation for patients who do not respond when the potential benefits are considered to outweigh any risks. • The use of sedating antihistamines as monotherapy is now less common because of concerns about reduced concentration and performance, but they can be effective and well tolerated by some individuals. • Doxepin has useful antihistaminic properties, but has sedating and anticholinergic side effects. • Addition of a sedating antihistamine at night (e.g., chlorphenamine, hydroxyzine) to a nonsedating antihistamine by day may help patients sleep better; however, it probably has little additional clinical effect on urticaria if the H₁ receptor is already saturated. <p><u>Antileukotriene agents</u></p> <ul style="list-style-type: none"> • Antileukotriene agents may be taken in addition to an H₁-antihistamine for poorly controlled urticaria; however, there is little evidence that they are useful as monotherapy. • Antileukotriene agents are more likely to benefit aspirin-sensitive and autologous serum skin test-positive chronic ordinary urticaria than other patterns of urticaria. Montelukast is usually chosen. <p><u>Corticosteroids</u></p> <ul style="list-style-type: none"> • Oral corticosteroids may shorten the duration of acute urticaria. • Parenteral hydrocortisone is often given as an adjunct for severe laryngeal edema and anaphylaxis although its action is delayed. Short courses of oral steroids over three to four weeks may be necessary for urticarial vasculitis and severe delayed pressure urticaria, but long-term oral corticosteroids should not be used in chronic urticaria except in select cases under regular specialist supervision. <p><u>Immunomodulating therapies</u></p> <ul style="list-style-type: none"> • Cyclosporin is the best studied immunosuppressive drug for chronic ordinary urticaria. Optimal patient selection, dose and duration of treatment still need to be defined. • Similar response rates have been seen with tacrolimus and mycophenolate mofetil. • Plasmapheresis and intravenous immunoglobulins may also be effective in severe autoimmune chronic urticaria.

Clinical Guideline	Recommendation(s)
<p>American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: Diagnosis and Management of Urticaria: A Practice Parameter (2014)³</p>	<ul style="list-style-type: none"> • There have been reports of success with methotrexate and cyclophosphamide. <p><u>Acute urticaria and angioedema</u></p> <ul style="list-style-type: none"> • Antihistamines are efficacious in most cases and are recommended as first-line therapy. Although first-generation antihistamines are rapidly acting and effective, in both pediatric and adult patients they may be associated with sedation and impaired motor skills due to their ability to cross the blood-brain barrier, while these impairments are less evident or not evident with second-generation antihistamines as a class. • In patients with poor response to antihistamines, a brief course of oral corticosteroids may also be required while attempting to eliminate suspected triggers and develop an effective treatment plan. <p><u>Chronic urticaria</u></p> <ul style="list-style-type: none"> • H₁-antagonists are effective in the majority of patients but may not achieve complete control in all patients. Second-generation antihistamines are safe and effective therapies in chronic urticaria and are considered first-line agents. • For patients not responding to monotherapy with a second generation antihistamine at Food and Drug Administration- approved doses, several treatment options can be employed. Higher doses of second-generation antihistamines may provide more efficacy but data are limited and conflicting for certain agents. Addition of H₂-antagonists or leukotriene receptor antagonists may be considered for patients with unsatisfactory responses to 2nd generation antihistamine monotherapy. First-generation antihistamines may also be considered in patients who do not achieve control of their condition with higher dose second-generation antihistamines. • Treatment with a potent antihistamine, hydroxyzine or doxepin, may be considered in patients who remain poorly controlled with dose advancement of second-generation antihistamines, and/or addition of one of more of the following: H₂-antihistamines, first-generation H₁-antihistamine at bedtime, and/or anti-leukotrienes. • Systemic corticosteroids are frequently used for refractory patients, but no controlled studies have demonstrated efficacy. In some patients, short-term use (e.g., one to three weeks duration) may be required to gain control of their disease until other therapies can achieve control. Because of the risk of adverse effects with systemic corticosteroids, long-term use for treatment of chronic urticaria patients should be avoided. Patients who are not adequately controlled on maximal antihistamine therapy may be considered to have refractory chronic urticaria. • A number of alternative therapies have been studied for the treatment of chronic urticaria; these therapies merit consideration for patients with refractory disease. <ul style="list-style-type: none"> ○ Omalizumab and cyclosporine have the greatest published experience for efficacy compared to all other alternative agents. The therapeutic utility of omalizumab for refractory chronic urticaria has been supported by findings from large double-blind randomized controlled trials and is associated with a relatively low rate of clinically significant adverse effects. ○ There is evidence from observational studies with cyclosporine, including long-term use that suggests cyclosporine is efficacious for refractory chronic urticaria and capable of inducing remission. There is also evidence for efficacy of cyclosporine from randomized controlled trials; however, taken in the context of study limitations, potential harms and cost, the quality of evidence from these randomized controlled trials supporting cyclosporine is low, leading to a weak recommendation for use of cyclosporine. ○ Many other alternative therapies have been used in refractory chronic urticaria; however the level of evidence supporting their use is lower than with omalizumab or cyclosporine. Anti-inflammatory agents including dapsone, sulfasalazine, hydroxychloroquine, and colchicine have limited

Clinical Guideline	Recommendation(s)
	<p>evidence for efficacy and some require laboratory monitoring for adverse effects. These agents are generally well tolerated and may be considered for properly selected patients with antihistamine refractory chronic urticaria. Other agents have been used in patients with refractory chronic urticaria, including but not limited to: theophylline, attenuated androgens, anticoagulants, NSAIDs, beta-agonists, cyclophosphamide, gold, plasmapheresis, cromolyn, and nifedipine; however, these agents should be reserved for patients with refractory urticaria who have failed other anti-inflammatory, immunosuppressant or biologic agents. Other unproven therapies, which are not recommended, include allergen immunotherapy, herbal therapies, vitamins, supplements, and acupuncture.</p>
<p>European Academy of Allergy and Clinical Immunology/ Global Allergy and Asthma European Network/ European Dermatology Forum/ World Allergy Organization: Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update (2013)¹⁵</p>	<p><u>Basic considerations</u></p> <ul style="list-style-type: none"> • The therapeutic approach to urticaria is universal (regardless of subtype) and based on the same principles as in other mast-cell-dependent diseases (elimination/avoidance of the cause or trigger, symptomatic pharmacological treatment, and inducing tolerance). • Acute urticaria differs from all other types as it is self-limited. Treatment is usually based on symptomatic relief. <p><u>Symptomatic pharmacological treatment</u></p> <ul style="list-style-type: none"> • Continuous treatment with H₁-antihistamines. • Recommendations are against the use of sedating (first-generation) antihistamines for the routine management of chronic urticaria as first-line agents. • Modern second-generation antihistamines (e.g., cetirizine, loratadine, fexofenadine) should be considered as the first-line symptomatic treatment for urticaria because of their good safety profile. • The majority of patients with urticaria not responding to single dose will profit from up-dosing of antihistamines. Modern second-generation antihistamines at licensed doses are first-line treatment in urticaria, and up-dosing is second-line treatment (up to fourfold dose). • A trial of omalizumab, cyclosporine A, or montelukast as add on therapy to modern second generation H₁-antihistamines is recommended as third-line therapy in treatment of urticaria. • Short course (maximum of 10 days) of corticosteroids may also be used as a third-line therapy or as an option for acute exacerbation. Long-term use of systemic corticosteroids is not recommended. • Antagonists of tumor necrosis factor-α (TNF-α) and IVIG, which have been successfully used in case reports, are recommended currently only to be used in specialized centers as last option (i.e., anti-TNF-α for delayed pressure urticaria and IVIG for chronic spontaneous urticaria).

III. Indications

The Food and Drug Administration (FDA)-approved indications for the first generation antihistamines are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the First Generation Antihistamines⁴

Generic Name(s)	Allergic Reactions to Blood/Plasma	Allergic Conjunctivitis	Allergic Rhinitis	Anaphylactic Reactions [†]	Angioedema*	Dermatographism	Sinusitis	Upper Respiratory Conditions [‡]	Urticaria*	Vasomotor Rhinitis
Ethanolamine Derivatives										
Carbinoxamine	✓	✓	✓	✓	✓	✓			✓	✓
Clemastine			✓		✓				✓	
Diphenhydramine [§]	✓	✓	✓	✓	✓	✓			✓	✓
Propylamine Derivatives										
Phenylephrine and chlorpheniramine			✓				✓	✓		

*Mild, uncomplicated allergic skin manifestations.

[†]Adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

[‡]Upper respiratory conditions may include the common cold.

[§]Diphenhydramine is also approved for Antiparkinsonism, insomnia, motion sickness, and for use as an antitussive.

IV. Pharmacokinetics

The pharmacokinetic parameters of the first generation antihistamines are listed in Table 4. There is insufficient information on the pharmacokinetic properties of the fixed-dose combination products. Therefore, only information on the individual components was included in the table.

Table 4. Pharmacokinetic Parameters of the First Generation Antihistamines¹⁶

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ethanolamine Derivatives					
Carbinoxamine	Good	Not reported	Liver	Renal	10 to 20
Clemastine	39	Not reported	Liver	Renal	21
Diphenhydramine	65 to 100	76 to 85	Liver (50)	Renal (50 to 65)	4 to 8
Propylamine Derivatives					
Chlorpheniramine	Good	Not reported	Liver, extensive	Renal (50)	20
Decongestants					
Phenylephrine	38	Not reported	Intestinal wall, extensive; Liver, moderate	Renal (80 to 86)	2 to 3

V. Drug Interactions

Significant drug interactions with the first generation antihistamines are listed in Table 5. Drug interactions are due to the individual components of the combinations products; therefore, only information on the individual ingredients was included in the table.

Table 5. Significant Drug Interactions with the First Generation Antihistamine¹⁶

Generic Name(s)	Interaction	Mechanism
Carbinoxamine	Monoamine oxidase inhibitors	Carbinoxamine anticholinergic effects (e.g., drying) may be increased and prolonged with monoamine oxidase inhibitor coadministration.
Carbinoxamine	CNS Depressants	Concurrent use may result in additive CNS effects.
Chlorpheniramine	Almotriptan	Concurrent use may result in increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Amitriptyline	Concurrent use may result in an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Amoxapine	Concurrent use may result in increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Fentanyl	Concurrent use may result in increased risk for serotonin syndrome and CNS depression.
Chlorpheniramine	Hydroxytryptophan	Concurrent use may result in increased risk of serotonin syndrome (hypertension, tachycardia, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Tramadol	Concurrent use may result in increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Trazodone	Concurrent use may result in increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Diphenhydramine	Linezolid	Concurrent use of diphenhydramine and linezolid may result in increased anticholinergic toxicity effects.

Generic Name(s)	Interaction	Mechanism
Phenylephrine	Monoamine oxidase inhibitors	Coadministration of a monoamine oxidase inhibitor and an indirect- or mixed-acting sympathomimetic may cause hypertensive crisis.
Phenylephrine	Linezolid	Pharmacologic effects of sympathomimetics may be increased by linezolid. Headache, hyperpyrexia, and hypertension may occur.
Phenylephrine	Rauwolfia alkaloids (e.g., reserpine)	Reserpine depletes stores of catecholamines, increasing the receptor sensitivity to the direct-acting sympathomimetics while antagonizing the effects of the indirect-acting agents which release norepinephrine from the neurons. Coadministration may result in hypertension.
Phenylephrine	Tricyclic antidepressants	Tricyclic antidepressants potentiate the pressor response of the direct-acting sympathomimetics; dysrhythmias have occurred. The pressor response to the indirect-acting sympathomimetics is decreased by the tricyclic antidepressants.

VI. Adverse Drug Events

The most common adverse drug events reported with the first generation antihistamines are listed in Table 6. These agents have the potential to cause sedation, performance impairment, and anticholinergic adverse effects.¹⁶

Table 6. Adverse Drug Events (%) Reported with the First Generation Antihistamines⁴

Adverse Events	Ethanolamine Derivatives			Propylamine Derivatives	Decongestants
	Carbinoxamine	Clemastine	Diphenhydramine	Chlorpheniramine	Phenylephrine
Cardiovascular					
Arrhythmias	-	-	-	-	✓
Bradycardia	-	✓	-	-	-
Cardiac dysrhythmia	-	-	-	✓	-
Cardiovascular finding	-	-	✓	-	-
Hypertension	-	-	-	-	✓
Hypotension	-	-	-	✓	-
Myocardial infarction	-	-	-	-	✓
Myocardial perfusion	-	-	-	-	✓
Pulmonary edema	-	-	-	-	✓
Raynaud's phenomenon	-	-	✓	-	-
Tachycardia	-	-	-	-	✓
Central Nervous System					
Anxiety	-	-	-	-	✓
Ataxia	-	✓	-	-	-
Central nervous system stimulation	-	✓	-	-	-
Dizziness	✓	✓	-	-	-
Drowsiness	-	✓	-	-	-
Dyskinesia	-	-	✓	✓	-
Dystonia	-	-	✓	-	-
Electro-encephalograph finding	-	-	-	✓	-
Encephalopathy	-	-	✓	-	-
Fatigue	✓	✓	-	-	-
Headache	✓	✓	-	-	-
Hypesthesia	-	-	-	-	✓
Insomnia	-	-	-	-	✓
Nervousness	✓	-	-	-	✓
Neurological finding	-	-	✓	-	-
Myofascial pain	-	-	-	-	✓
Sedation	✓	-	-	✓	-
Somnolence	-	✓	✓	✓	-

Adverse Events	Ethanolamine Derivatives			Propylamine Derivatives	Decongestants
	Carbinoxamine	Clemastine	Diphenhydramine	Chlorpheniramine	Phenylephrine
Vertigo	-	✓	-	-	-
Dermatologic					
Contact dermatitis	✓	-	-	✓	✓
Dermatitis	-	-	✓	-	-
Dermatologic finding	-	-	✓	-	-
Phototoxicity	-	-	✓	-	-
Pruritus	-	✓	-	-	-
Rash	-	✓	-	-	-
Endocrine/Metabolic Effects					
Acute intermittent porphyria	-	✓	✓	-	-
Gastrointestinal					
Anorexia	✓	-	-	✓	-
Constipation	-	-	-	✓	-
Diarrhea	✓	-	-	✓	-
Dry mouth	✓	✓	-	-	-
Epigastric distress	-	-	-	✓	-
Gastric pain	-	✓	-	-	-
Heartburn	✓	-	-	-	-
Nausea	✓	✓	-	✓	-
Vomiting	✓	✓	-	✓	-
Hematologic					
Agranulocytosis	-	-	-	✓	-
Aplastic anemia	-	-	-	✓	-
Leukocytosis	-	-	-	-	✓
Thrombocytopenia	-	-	-	✓	-
Immunologic					
Anaphylaxis	-	-	✓	-	-
Cell-mediated immune reaction	-	-	-	-	✓
Immune hypersensitivity reaction	-	-	✓	-	-
Immune system finding	-	-	✓	-	-
Musculoskeletal					
Fracture of bone	-	-	✓	-	-
Musculoskeletal finding	-	-	✓	-	-
Myasthenia gravis	-	-	✓	-	-
Ophthalmic					
Aqueous pigment floater	-	-	-	-	✓

Adverse Events	Ethanolamine Derivatives			Propylamine Derivatives	Decongestants
	Carbinoxamine	Clemastine	Diphenhydramine	Chlorpheniramine	Phenylephrine
Conjunctivitis	-	-	-	-	✓
Diplopia	✓	-	-	-	-
Miosis	-	-	-	-	✓
Mydriasis	-	-	-	-	✓
Psychiatric					
Agitation	✓	-	-	-	-
Excitability	✓	-	✓	-	-
Hallucinations	✓	-	-	✓	✓
Motor nervous system finding	-	-	✓	-	-
Panic	-	-	-	-	✓
Paranoid delusions	-	-	-	-	✓
Psychiatric sign or symptom	-	-	✓	-	-
Psychosis	-	-	-	-	✓
Psychotic disorder	-	-	✓	-	-
Toxic psychosis	-	-	-	-	✓
Renal					
Dysuria	✓	-	-	-	-
Polyuria	✓	-	-	-	-
Urogenital finding	✓	-	-	-	-
Respiratory					
Nasal dryness	✓	-	-	-	-
Pulmonary edema	-	-	-	-	✓
Pulmonary embolism	-	-	-	-	✓
Respiratory finding	-	-	✓	-	-
Shortness of breath	-	✓	-	-	-
Other					
Anticholinergic effects	-	-	✓	-	-
Death	-	-	✓	-	-
Drug abuse	-	-	✓	-	-
Drug dependence	-	-	✓	-	-
Sense of smell altered	-	-	-	-	✓
Withdrawal sign or symptom	-	-	✓	-	-

✓ Percent not specified.
 - Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the first generation antihistamines are listed in Table 7. Due to the differences in dosing with the various salt formulations, the products have been further classified by salt formulation in this table when necessary.

Table 7. Usual Dosing Regimens for the First Generation Antihistamines^{4,17}

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ethanolamine Derivatives			
Carbinoxamine	<u>Allergic rhinitis and other allergic conditions:</u> Solution, tablet: 4 to 8 mg three to four times daily	<u>Allergic rhinitis and other allergic conditions:</u> Solution, tablet: ≥12 years of age: 4 to 8 mg three to four times daily 6 to 11 years of age: 2 to 4 mg three to four times daily Solution: 6 to 11 years of age: 2 to 4 mg three to four times daily; 2 to 5 years of age: 1 to 2 mg three or four times daily	Solution: 4 mg/5 mL Tablet: 4 mg
Clemastine	<u>Allergic rhinitis:</u> Syrup, tablet: initial, 1.34 mg two times daily or 2.68 mg as a single dose; maximum, 8.04 mg/day <u>Allergic urticaria and angioedema:</u> Syrup, tablet: initial, 2.68 mg one to three times daily; maximum, 8.04 mg/day <u>Upper respiratory conditions:</u> Syrup, tablet: 1.34 mg two times daily; maximum, 2.68 mg/day	<u>Allergic rhinitis:</u> Syrup, tablet: ≥12 years of age: initial, 1.34 mg two times daily; maximum, 8.04 mg/day; 6 to <12 years of age: initial, 0.67 mg two times daily; maximum, 4.02 mg/day <u>Allergic urticaria and angioedema:</u> Syrup, tablet: ≥12 years of age: initial, 2.68 mg one to three times daily; maximum, 8.04 mg/day; 6 to <12 years of age: initial, 1.34 mg two times daily; maximum, 4.02 mg/day <u>Upper respiratory conditions:</u> Syrup, tablet: ≥12 years of age: 1.34 mg two times daily; maximum, 2.68 mg/day	Syrup: 0.67 mg/5 mL Tablet: 2.68 mg
Diphenhydramine	<u>Allergic rhinitis and upper respiratory conditions:</u> Oral: 25 to 50 mg four to six times daily; maximum, 300 mg/day <u>Antitussive:</u> Oral: 25 mg six times daily; maximum, 150 mg/day <u>Insomnia:</u> Oral: 50 mg at bedtime <u>Motion sickness:</u> Oral: 25 to 50 mg four to six times daily; maximum, 300	<u>Allergic rhinitis and upper respiratory conditions:</u> Oral: ≥12 years of age: 25 to 50 mg four to six times daily; maximum, 300 mg/day; 6 to <12 years of age: 12.5 to 25 mg four to six times daily; maximum, 150 mg/day <u>Antitussive:</u> Oral: ≥12 years of age: 25 mg four to six times daily; maximum, 150 mg/day <u>Motion sickness:</u> Oral: ≥12 years of age: 25 to 50	Elixir: 12.5 mg/5 mL Injection: 50 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg/day <u>Parkinsonian syndrome:</u> Oral: initial, 25 mg three times daily; maintenance, 50 mg four times daily <u>Other:</u> Injection: 10 to 15 mg IM or IV; maximum, 400 mg/day	mg four to six times daily; maximum, 300 mg/day; 6 to <12 years of age: 12.5 to 25 mg 30 to 60 minutes prior to travel and four to six times daily; maximum, 150 mg/day; 2 to <6 years of age: 6.25 mg 30 to 60 minutes prior to travel and four to six times daily; maximum, 37.5 mg/day <u>Insomnia:</u> Oral: ≥12 years of age: 1 mg/kg 30 minutes prior to bedtime; maximum, 50 mg/day <u>Other:</u> Injection: 5 mg/kg/day or 150 mg/m ² IM or IV; maximum, 300 mg/day	
Propylamine Derivatives			
Phenylephrine HCl and chlorpheniramine maleate	<u>Antihistamine/Decongestant:</u> Drops (2-1 mg/mL): four mL four to six times daily; maximum, 24 mL per day	<u>Antihistamine/Decongestant:</u> Drops (2-1 mg/mL): ≥12 years of age: four mL four to six times daily; maximum, 24 mL per day; 6 to <12 years of age: two mL four to six times daily; maximum, 8 to 12 mL per day	Drops: 2-1 mg/mL

HCl=hydrochloride, IM=intramuscular, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the first generation antihistamines are summarized in Table 8.

Table 8. Comparative Clinical Trials with the First Generation Antihistamines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Allergic Rhinitis				
Druce et al. ¹⁸ (1998) Brompheniramine ER 12 mg BID vs loratadine 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients >12 years of age with allergic rhinitis	N=338 7 days	Primary: Global evaluation scores, evaluation of symptom relief, total symptom severity scores, nasal symptom scores, adverse events Secondary: Not reported	Primary: At day three and day seven, physician and subject global evaluation scores for brompheniramine were significantly better than those for loratadine (P<0.001) and placebo (P<0.001). Loratadine was more effective than placebo; however, this was not statistically significant. On the subjects' daily overall evaluations of symptom relief, brompheniramine was significantly better than loratadine and placebo on all seven days (P value not reported). Loratadine was significantly better than placebo on day four. The total symptom severity scores improved to a greater degree with brompheniramine compared to loratadine or placebo at day three, day seven, and the average over the two visits (P<0.05). Treatment with loratadine improved symptoms to a greater degree than placebo (P<0.05 only when symptoms were averaged over day three and day seven). The mean individual symptom severity scores paralleled the pattern seen for the summed symptom severity scores in the three groups. Improvement in nasal symptoms was significantly greater in the patients taking brompheniramine than in those taking loratadine (P<0.01) or placebo (P<0.001) at day three, day seven, and when averaged over the two visits. Improvement in nasal symptoms in the loratadine treatment group was greater than that in the placebo treatment group at day three (P<0.05). At visit two, adverse events were reported by 53% of the patients taking brompheniramine, 33% of those taking loratadine, and 36% of those taking placebo (P=0.006). At visit three, adverse events were reported by 34% of the patients taking brompheniramine, 20% of those taking loratadine, and 29% of those taking placebo (P=0.05). At visit two, the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>frequency of somnolence was 28, 9, and 6% in the brompheniramine, loratadine, and placebo groups, respectively (P<0.001). At visit three, the frequency of somnolence was reduced to 10, 2, and 3% for the brompheniramine, loratadine, and placebo groups, respectively (P=0.011).</p> <p>Secondary: Not reported</p>
<p>Crawford et al.¹⁹ (1998)</p> <p>Chlorpheniramine 8 mg BID for 2 weeks</p> <p>vs</p> <p>astemizole 10 mg QD for 2 weeks</p> <p>vs</p> <p>loratadine 10 mg QD for 2 weeks</p> <p>vs</p> <p>terfenadine† 60 mg BID for 2 weeks</p> <p>Pseudoephedrine 60 mg every 8 hours as needed was permitted throughout the study.</p>	<p>OL, XO</p> <p>Patients with perennial allergic rhinitis</p>	<p>N=14</p> <p>8 weeks</p>	<p>Primary: Nasal-examination score, rhinitis symptom score, overall efficacy score, pseudoephedrine use, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: The physician assessed nasal-examination score for each of the four antihistamines was significantly better than the baseline nasal-examination score (P<0.05).</p> <p>The nasal-examination score for astemizole was significantly better than loratadine (P<0.05). No other significant differences in nasal-examination score were noted among the treatment groups.</p> <p>There were no significant differences among antihistamines when comparing patient-reported rhinitis symptom scores, overall efficacy scores, or pseudoephedrine use.</p> <p>Sedation was noted most frequently by patients taking chlorpheniramine. Headache was the most frequent adverse event with terfenadine.</p> <p>Secondary: Not reported</p>
<p>von Maur et al.²⁰ (1985)</p>	<p>OL</p>	<p>N=782</p>	<p>Primary: Patient preference</p>	<p>Primary: The order of antihistamine preference was chlorpheniramine,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Chlorpheniramine 2 to 4 mg QID for 2 weeks</p> <p>vs</p> <p>diphenhydramine 12.5 to 25 mg QID for 2 weeks</p> <p>vs</p> <p>hydroxyzine 10 to 25 mg QID for 2 weeks</p> <p>vs</p> <p>tripelennamine† 37.5 to 50 mg TID for 2 weeks</p> <p>vs</p> <p>trimeprazine† 2.5 mg TID for 2 weeks</p>	<p>Adults and children with seasonal or perennial allergic rhinitis</p>	<p>5 years</p>	<p>and long-term choice of antihistamine</p> <p>Secondary: Not reported</p>	<p>diphenhydramine, tripelemnamine, hydroxyzine, and trimeprazine (P<0.001).</p> <p>At the end of one year, 78% of patients remained on their preferred antihistamine. By three years, 71% of patients were still on the antihistamine of first choice. By five years, 57% of patients were still on the antihistamine class that had been selected five years before.</p> <p>Secondary: Not reported</p>
<p>Prevost et al.²¹ (1994)</p> <p>Chlorpheniramine 12 mg and pseudoephedrine 120 mg BID</p> <p>vs</p>	<p>DB, MC, PG, RCT</p> <p>Patients 18 to 65 years of age with seasonal allergic rhinitis</p>	<p>N=134</p> <p>14 days</p>	<p>Primary: Nasal and non-nasal symptoms</p> <p>Secondary: Not reported</p>	<p>Primary: There was a significant decrease from baseline in mean TTSs in both treatment groups (P<0.01).</p> <p>On day three, improvement in mean TSS was 54% in the loratadine/pseudoephedrine group and 57% in the chlorpheniramine/pseudoephedrine group. On day 14, there was a 65% improvement in the patients treated with loratadine/pseudoephedrine and 64% improvement in the chlorpheniramine/pseudoephedrine group.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>loratadine 5 mg and pseudoephedrine 120 mg BID</p> <p>Products were ER fixed-dose combinations.</p>				<p>Reduction in mean total nasal and non-nasal symptom scores was comparable between the two treatment groups. By day 14, nasal symptom improvement was 60% in the loratadine/pseudoephedrine group and 61% in the chlorpheniramine/pseudoephedrine group. Improvement was comparable for nasal discharge (53 vs 45%, respectively), stuffiness (52 vs 44%, respectively), and sneezing (61 vs 54%, respectively) on day three.</p> <p>Improvement in mean total non-nasal symptom scores was comparable and not significantly different between the two treatment groups on day three (P value not reported). At day 14, improvement in non-nasal symptom scores was 69% in both study groups. Patients in the chlorpheniramine/pseudoephedrine group showed greater relief of red eyes at day three (63 vs 54%) and day 14 (75 vs 68%). Patients treated with loratadine/pseudoephedrine showed greater improvement in ear/palate itch (60 vs 50%) at day 14.</p> <p>The most frequently reported side effects were headache (16% in both groups) and insomnia (16% in the loratadine/pseudoephedrine group and 18% in the chlorpheniramine/pseudoephedrine group). There was a greater incidence of fatigue (6 vs 25%, P<0.01), dry mouth (7 vs 19%; P=0.07), and sedation (7 vs 22%; P<0.03) in the group receiving chlorpheniramine/pseudoephedrine compared to those receiving loratadine/pseudoephedrine.</p> <p>Secondary: Not reported</p>
<p>Gibbs et al.²² (1998)</p> <p><u>Study 2</u></p> <p>Clemastine 1.34 mg TID for 5 days</p> <p>vs</p> <p>acrivastine 8 mg</p>	<p>RCT, XO</p> <p>Adults with seasonal allergic rhinitis</p>	<p>N=54</p> <p>21 days</p>	<p>Primary: Nasal and non-nasal symptoms</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Study 2</i></p> <p>The acrivastine was significantly better than placebo for the relief of itchy nose, blocked nose and watery eyes symptoms, and for calculated overall symptom score (mean of all seven symptoms). Clemastine was significantly better than placebo for alleviation of the symptoms of itchy nose, running nose, itchy eyes and watery eyes, and for calculated overall symptom score. There were no significant differences between the two antihistamines.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>TID for 5 days</p> <p>vs</p> <p>placebo for 5 days</p> <p><u>Study 1</u></p> <p>Acrivastine 4 mg TID for 5 days</p> <p>vs</p> <p>acrivastine 8 mg TID for 5 days</p> <p>vs</p> <p>placebo for 5 days</p>				<p>In study 2, drowsiness was reported by seven (39%) patients receiving clemastine compared to one patient receiving acrivastine (P<0.05).</p> <p><i>Study 1</i></p> <p>High- and low-dose acrivastine led to significantly lower scores than placebo for all symptoms, except blocked nose (P>0.01). There was no significant difference in symptom scores between the two doses of acrivastine.</p> <p>Sixty-three percent of patients rated symptom control as excellent or good during treatment with 8 mg acrivastine compared with 46% for 4 mg acrivastine and 36% for placebo (8 mg acrivastine vs placebo; P=0.058).</p> <p>There were no statistically significant differences in the proportion of patients who would have requested further treatment had it been available on prescription although slightly more patients on 4 mg acrivastine (61%) and 8 mg acrivastine (62%) than on placebo (54%) indicated this desire. Only 20% of patients preferred treatment with placebo. This is compared to 40% of patients preferring acrivastine 4 mg and 40% preferring acrivastine 8 mg.</p> <p>Secondary: Not reported</p>
<p>Sheriff et al.²³ (1976)</p> <p>Clemastine 1.34 mg given as 1 to 2 tablets 2 to 3 times daily</p> <p>vs</p> <p>chlorpheniramine 4 mg given as 1 to 2 tablets 2 to 3 times daily</p>	<p>DB, PG, RCT</p> <p>Patients 7 to 40 years of age with seasonal allergic rhinitis</p>	<p>N=51</p> <p>2 weeks</p>	<p>Primary: Mean total number of tablets taken, mean TSSs, mean number of days the patient felt drowsy, investigator's and patient's assessment of effectiveness of treatment</p> <p>Secondary: Not reported</p>	<p>Primary: The mean number of tablets taken was similar with clemastine (27.8) and chlorpheniramine (28.1; P value not significant).</p> <p>The mean TSSs were similar with clemastine (16.2) and chlorpheniramine (14.0; P value not significant).</p> <p>The mean number of days drowsy was similar with clemastine (1.58) and chlorpheniramine (1.08; P value not significant).</p> <p>The effectiveness of clemastine and chlorpheniramine as defined by the investigator's assessments and by the patients' daily record forms were similar among the two treatment groups.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Thomas et al.²⁴ (1977)</p> <p>Clemastine 2.68 mg as a single dose</p> <p>vs</p> <p>chlorpheniramine 4 mg as a single dose</p> <p>vs</p> <p>placebo</p>	<p>DB, RCT</p> <p>Patients >15 years of age with seasonal allergic rhinitis</p>	<p>N=46</p> <p>1 day</p>	<p>Primary: Alteration in airway resistance, nasal congestion, nasal obstruction, nasal airway patency, investigator's and patient's subjective assessments of improvement</p> <p>Secondary: Not reported</p>	<p>Secondary: Not reported</p> <p>Primary: Treatment with clemastine and chlorpheniramine resulted in significant changes in the plethysmographic oral resistance evaluations compared to baseline. There were no significant differences noted with placebo compared to baseline. Clemastine was significantly better than placebo for hours two and six (P<0.10) and for the mean response over all time points (P<0.05). There were no significant differences for patients receiving chlorpheniramine compared to placebo.</p> <p>Differences in nasal resistance and total airway resistance among the three treatment groups were not significant.</p> <p>Treatment with clemastine and chlorpheniramine resulted in significant improvements in nasal congestion compared to baseline. Both clemastine and chlorpheniramine also demonstrated greater improvements in nasal congestion compared to placebo at all time points and overall (P<0.05).</p> <p>There were no significant differences in nasal obstruction among the three treatment groups.</p> <p>Treatment with clemastine and chlorpheniramine led to improvements in the investigator's subjective evaluation of nasal congestion at each time point. There was no difference noted with placebo. More patients treated with clemastine showed improvement (64 to 73%) compared to placebo (9 to 18%; P<0.05). There was no significant difference in nasal congestion with chlorpheniramine compared to placebo.</p> <p>There were no significant differences in the overall improvement index of physician-evaluated signs among the three treatment groups.</p> <p>Patients' self-evaluation of changes in symptoms showed improvement in all treatment groups.</p> <p>The most common adverse reaction was drowsiness. The number of patients with severe drowsiness was higher in the chlorpheniramine group</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				than in the placebo group (P<0.10). Secondary: Not reported
Todd et al. ²⁵ (1975) <u>Study 1</u> Clemastine 1.34 mg BID to QID vs chlorpheniramine 4 mg BID to QID <u>Study 2</u> Clemastine elixir 0.5 mg BID vs chlorpheniramine syrup 2 mg BID	DB, PG, RCT <u>Study 1</u> Adults with allergic rhinitis <u>Study 2</u> Children with allergic rhinitis	<u>Study 1</u> N=58 3 weeks <u>Study 2</u> N=42 3 weeks	Primary: Physician's assessment of improvement after treatment Secondary: Not reported	Primary: <i>Study 1</i> In the physician's assessment of improvement, 50% of clemastine-treated patients were to be greatly improved compared to 23% (improved), 13% (no change), and 13% (worse). This is compared to 28% of patients in the chlorpheniramine group who were considered to be greatly improved, 43% (improved), 14% (no change), and 14% (worse). There were no P values reported. Adverse events were minimal with both preparations. Drowsiness when reported was mainly of a transient nature with no significant difference in incidence or severity between the compounds. <i>Study 2</i> In the physician's assessment of improvement, 32% of clemastine-treated patients were to be greatly improved compared to 21% (improved), 11% (no change), and 32% (worse). This is compared to 31% of patients in the chlorpheniramine group who were considered to be greatly improved, 13% (improved), 4% (no change), and 52% (worse). There were no P values reported. There were no reports of drowsiness or tiredness from any of the 19 patients receiving clemastine. Of the 23 patients receiving chlorpheniramine, three complained of drowsiness. Secondary: Not reported
Dockhorn et al. ²⁶ (1987) Clemastine 1.34 mg BID	DB, MC, PC, PG, RCT Patients with seasonal allergic rhinitis	N=330 14 days	Primary: Assessment of nasal and non-nasal symptoms, overall condition or rhinitis, and	Primary: Improvement in mean total symptoms scores and nasal symptom scores were significantly greater with loratadine and clemastine than placebo at each time point (P<0.01). There was no significant difference between the loratadine and clemastine treatment groups (P value not significant) at day three, day 14, or study end point. At day seven, the improvement in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs loratadine 10 mg QD vs placebo			therapeutic response to treatment Secondary: Not reported	<p>loratadine group was significantly greater than that of the clemastine group (P=0.04 for TSSs and P=0.05 for nasal symptom scores). Non-nasal symptom scores were not reported.</p> <p>In the physician evaluation of therapeutic response, loratadine and clemastine led to a more favorable response to treatment than placebo. By day three, an excellent response was seen in 22% of loratadine-treated patients, 9% of the clemastine-treated patients, and 3% of the placebo-treated patients. Likewise, 22, 43, and 23%, respectively, were rated as have a good response to treatment. In the end point analysis, the percentage of patients with a good or excellent response to treatment was 29 and 27%, respectively with loratadine; 13 and 42%, respectively with clemastine; 5 and 27%, respectively with placebo.</p> <p>A greater percentage of patients reported at least one adverse event with clemastine (37%) than with loratadine (21%) or placebo (20%; P<0.01). Sedation was reported by a greater percentage of patients receiving clemastine (22%) than loratadine (6%) or placebo (5%; P<0.01). There was no difference in dry mouth among the treatment groups.</p> <p>Secondary: Not reported</p>
Frølund et al. ²⁷ (1990) Clemastine 1.34 mg BID vs loratadine 10 mg QD vs placebo	DB, MC, PG, RCT Patients 18 to 65 years of age with perennial allergic rhinitis	N=155 3 weeks	Primary: Total, nasal and non-nasal symptom severity Secondary: Not reported	<p>Primary: The loratadine and clemastine groups showed a significant improvement compared to placebo when nasal membranes, secretion, and patency were assessed with rhinoscopy (P<0.05).</p> <p>Loratadine and clemastine significantly reduced patients' total nasal and total eye symptoms compared to placebo (P<0.05). A similar reduction was seen for all four nasal symptoms (discharge, stuffiness, itching, and sneezing). For eye symptoms, this decrease was found for redness and itching (P<0.05), but no significant decrease was observed for tearing.</p> <p>Loratadine improved total symptoms scores at day seven compared to clemastine (P<0.05). Loratadine also improved nasal itching and nasal stuffiness more effectively than clemastine at day seven (P<0.05). There were no significant changes between the treatment groups at other time</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>points.</p> <p>The diary cards showed there was a significant onset of relief of symptoms within the first day of treatment with loratadine and clemastine compared to placebo. A faster onset of symptom relief was also seen in the loratadine group compared with the clemastine group within the first day (P<0.05).</p> <p>There were fewer adverse events reported with loratadine compared to clemastine (P<0.05) and placebo (P<0.05).</p> <p>Secondary: Not reported</p>
<p>Irander et al.²⁸ (1990)</p> <p>Clemastine 1.34 mg BID</p> <p>vs</p> <p>loratadine 40 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, RCT</p> <p>Patients >18 years of age with a history of rhino-conjunctivitis during the birch pollen season</p>	<p>N=107</p> <p>2 weeks</p>	<p>Primary: Rhino-conjunctivitis symptoms</p> <p>Secondary: Not reported</p>	<p>Primary: Loratadine significantly reduced all rhino-conjunctivitis symptoms compared to placebo, except for nasal stuffiness (P value not significant).</p> <p>Clemastine significantly reduced sneezing, nasal discharge, and tearing compared to placebo; however, there was no difference in nasal itching/stuffiness, ocular itching/redness, or palatal itching (P value not significant).</p> <p>There was no significant difference in the majority of the rhino-conjunctivitis symptoms between clemastine and loratadine, except for ocular itching/redness (P<0.05).</p> <p>Sedation was the most common adverse event. There was no difference in sedation with loratadine compared to placebo; however, a significantly higher incidence was noted in patients treated with clemastine (P<0.05). Dizziness, headache, insomnia, dryness of the mouth and nausea were reported rarely.</p> <p>Secondary: Not reported</p>
<p>Boner et al.²⁹ (1989)</p>	<p>RCT</p> <p>Children 4 to 12</p>	<p>N=40</p> <p>14 days</p>	<p>Primary: Symptom severity</p>	<p>Primary: Symptom severity (on physical exam and subjective symptoms) improved with both drugs during the 14-day treatment period (P<0.01). There was</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Dex-chlorpheniramine 1 mg every 8 hours</p> <p>vs</p> <p>loratadine 5 mg QD</p> <p>Children under 6 years and those weighing less than 20 kg received half the dose.</p>	<p>years of age with moderate-to-severe seasonal allergic rhinitis</p>		<p>Secondary: Not reported</p>	<p>no significant difference between the dexchlorpheniramine or loratadine treatment groups (P=0.295).</p> <p>Rhinoscopy showed a reduction in nasal secretions/stuffiness with both treatments and there was no significant difference between the treatment groups (P value not significant).</p> <p>The evaluation of therapeutic results by both the investigator and the patient/parent had similar positive results with both drugs at each visit (P>0.05).</p> <p>Four children receiving dexchlorpheniramine had somnolence on day one, two other patients complained of mild epistaxis during the first three days of treatment. Two children in the loratadine group had two episodes of moderate epistaxis, one on days one to two and the other on days six to eight, no child reported drowsiness.</p> <p>Secondary: Not reported</p>
<p>Raphael et al.³⁰ (2006)</p> <p>Diphenhydramine 50 mg TID</p> <p>vs</p> <p>desloratadine 5 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 12 to 65 years of age with moderate-to-severe seasonal allergic rhinitis</p>	<p>N=610</p> <p>1 week</p>	<p>Primary: Change from baseline in the TNSS</p> <p>Secondary: Change from baseline in TSS, individual symptom scores, global evaluation of response to treatment</p>	<p>Primary: Diphenhydramine had a 46.7% greater reduction in patient TNSSs compared with desloratadine (-1.81; P<0.001). Investigator TNSS results were similar to those recorded by patients.</p> <p>Secondary: Diphenhydramine had a 45.5% greater reduction in patient TSS compared with desloratadine (-3.35; P<0.001). Investigator TSS results were similar to those recorded by patients.</p> <p>Treatment with diphenhydramine led to significant reductions in all eight individual symptom scores compared to placebo and desloratadine, including nasal congestion. Treatment with desloratadine led to a greater reduction in six of the eight individual symptoms compared to placebo (nasal congestion, rhinorrhea, sneezing, nasal itching, redness of eyes, and itching ears/palate); however, only sneezing was significant (-0.27; P=0.04). Similar results were observed for investigator-scored individual symptoms.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>The daily nasal congestion scores were significantly reduced with diphenhydramine compared to desloratadine and placebo throughout the seven-day treatment period.</p> <p>Percentage improvement in the patient mean global response to treatment scores over placebo were 134.5% (P<0.001) for diphenhydramine and 29.4% (P=0.20) for desloratadine. Diphenhydramine had an 81.2% (P<0.001) greater improvement in the patient mean global response to treatment score compared with desloratadine.</p> <p>Adverse events were observed in 35.3, 16.3, and 8.3% of patients who received diphenhydramine, desloratadine, and placebo, respectively. The most common adverse events were somnolence, dry mouth, asthenia, headache, and dizziness.</p>
<p>Park et al.³¹ (2011)</p> <p>Diphenhydramine 1 mg/kg</p> <p>vs</p> <p>cetirizine 0.25 mg/kg</p>	<p>DB, RCT</p> <p>Patients 3 to 19 years of age experiencing an allergic reaction during oral food challenge</p>	<p>N=64</p> <p>70 allergic reactions</p> <p>Duration not specified</p>	<p>Primary: Proportion of patients experiencing sedation (sedation score of 1 or 2)</p> <p>Secondary: Mean resolution of urticaria and pruritus, administration of other medications</p>	<p>Primary: Overall, 28.6 and 17.1% of patients receiving diphenhydramine and cetirizine experienced sedation, reflecting a nonsignificant difference in sedation of 11.4% (95% CI, -8.4 to 30.2%).</p> <p>Secondary: The mean time to resolution of urticaria and pruritus was similar between the two treatments. Among patients receiving diphenhydramine, mean time to resolution was 42.3±13.15 minutes compared to 40.8±22.11 minutes among patients receiving cetirizine (P=0.86). For pruritus the corresponding times were 28.6±20.54 and 31.3±20.07 minutes (P=0.67). Furthermore, the mean time to first onset of resolution of urticaria and pruritus was similar between the two treatments.</p> <p>There was no difference in the administration of other medications between the two treatments. Other treatments included steroid and/or epinephrine.</p>
<p>Connell et al.³² (1982)</p> <p>Triprolidine 2.5 mg and</p>	<p>DB, PC, RCT</p> <p>Patients >16 years of age with seasonal allergic rhinitis</p>	<p>N=184</p> <p>2 days</p>	<p>Primary: TARs, nasal congestion scores, hay fever symptom complex score,</p>	<p>Primary: There was no difference in the mean TARs among the four treatment groups. Triprolidine/pseudoephedrine was better than triprolidine (P≤0.025) at 12.30 hours, 13.30 hours and 15.30 hours (borderline) on Day 1, and at 15.30 hours on Day 2.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>pseudoephedrine 60 mg given every 6 hours as a fixed-dose combination</p> <p>vs</p> <p>triprolidine 2.5 mg given every 6 hours</p> <p>vs</p> <p>pseudoephedrine 60 mg given every 6 hours</p> <p>vs</p> <p>placebo</p>			<p>patient's perception of overall therapeutic benefit</p> <p>Secondary: Not reported</p>	<p>For the end point of mean nasal congestion scores vs hour after dosing, triprolidine/pseudoephedrine was better ($P \leq 0.025$) than: (1) triprolidine at 13.30 hours and 15.30 hours on Day 2; and (2) placebo at 10.30 hours, 11.30 hours (borderline), 12.30 hours (borderline), 13.30 hours (borderline), 14.30 hours, 15.30 hours (borderline), and 16.30 hours on Day 2.</p> <p>For the end point of hay fever symptom complex score, triprolidine/pseudoephedrine was better ($P \leq 0.025$) than: (1) pseudoephedrine at 12.30-14.30 hours, and 16.30 hours on Day 1, and at 13.30 hours (borderline), 15.30 and 16.30 hours on Day 2; and (2) placebo at 12.30-14.30 hours, and 15.30 hours (borderline) on Day 1, and at 08.30 hours, 10.30-11.30 hours (borderline) and 12.30-16.30 hours on Day 2. The mean symptom complex score was also better with triprolidine/pseudoephedrine compared to pseudoephedrine and placebo ($P = 0.01$, respectively).</p> <p>The patients' perception of overall therapeutic benefit was assessed at 08.30 hours on Day 2 by the question "Did the medication help?" For patients receiving triprolidine/pseudoephedrine, 52% said they noticed marked improvement compared to those receiving triprolidine (22%), pseudoephedrine (17%), or placebo (9%).</p> <p>The three most frequently reported adverse events were dry nose, drowsiness and headache.</p> <p>Secondary: Not reported</p>
<p>Diamond et al.³³ (1981)</p> <p>Tripolidine 2.5 mg and pseudoephedrine 60 mg as a fixed-dose combination</p>	<p>DB, PC, RCT</p> <p>Patients >18 years of age with seasonal allergic rhinitis</p>	<p>N=151</p> <p>1 day</p>	<p>Primary: NAR, symptom complex score, nasal congestion score, adverse events</p> <p>Secondary:</p>	<p>Primary: Treatment with triprolidine/pseudoephedrine resulted in a greater reduction in NAR compared to triprolidine at all time points after one hour ($P \leq 0.025$) and a greater reduction in NAR compared to placebo at hours six and seven ($P \leq 0.025$). There was no statistical comparison with pseudoephedrine alone for this end point. When the area under the NAR-time curves were compared, the overall response to treatment was greater with triprolidine/pseudoephedrine than triprolidine or placebo ($P \leq 0.025$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>given at 10:00 AM, 1:00 PM, and 4:00 PM (3 doses)</p> <p>vs</p> <p>triprolidine 2.5 mg given at 10:00 AM, 1:00 PM, and 4:00 PM (3 doses)</p> <p>vs</p> <p>pseudoephedrine 60 mg given 10:00 AM, 1:00 PM, and 4:00 PM (3 doses)</p> <p>vs</p> <p>placebo</p>			<p>Not reported</p>	<p>Reduction in the nasal congestion scores were greater with triprolidine/pseudoephedrine compared to placebo (hours six, seven and eight; $P \leq 0.025$) and triprolidine (hours six and eight; $P \leq 0.025$). There was no difference in nasal congestion scores between triprolidine/pseudoephedrine and pseudoephedrine alone.</p> <p>For the end point of symptom complex scores, triprolidine/pseudoephedrine resulted in a greater reduction in symptoms compared to pseudoephedrine alone at hours three, six, seven and eight and a greater reduction in symptoms compared to placebo at hours three, four, six, seven and eight ($P \leq 0.025$, respectively). The mean symptom complex score was also better with triprolidine/pseudoephedrine compared to pseudoephedrine and placebo ($P \leq 0.025$, respectively). There was no difference in symptom complex scores between triprolidine/pseudoephedrine and triprolidine alone.</p> <p>Drowsiness was the most frequently reported adverse event.</p> <p>Secondary: Not reported</p>
<p>Empey et al.³⁴ (1975)</p> <p>Tripolidine 2.5 mg and pseudoephedrine 60 mg TID for 2 weeks</p> <p>vs</p> <p>triprolidine 2.5 mg TID for 2 weeks</p> <p>vs</p>	<p>DB, PC, XO</p> <p>Adults with seasonal allergic rhinitis</p>	<p>N=40</p> <p>10 weeks</p>	<p>Primary: Symptoms (daily diary card), patient's overall impression of improvement, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: The mean number of days sneezing occurred was lower with triprolidine/pseudoephedrine (4.05 days) compared to triprolidine (6.1 days), pseudoephedrine (6.53 days) and placebo (7.33 days; $P < 0.05$ for all comparisons). Triprolidine/pseudoephedrine was also more effective than pseudoephedrine and placebo in reducing the severity of sneezing ($P < 0.05$). There was no difference in severity of sneezing between triprolidine/pseudoephedrine and triprolidine alone.</p> <p>The three active treatment groups were more effective than placebo in reducing the number of days of rhinorrhea and eye irritation occurred, as well as the severity of these symptoms ($P < 0.05$ for all comparisons with placebo). There were no significant differences noted among the three active treatment groups.</p> <p>There was no significant difference in the number of days of nasal</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>pseudoephedrine TID for 2 weeks</p> <p>vs</p> <p>placebo for 2 weeks</p>				<p>blockage, or the severity of this symptom, among the 4 treatment groups.</p> <p>Overall scores on the “better or worse than usual” assessment and the patient’s choices of “best or joint best period” showed triprolidine/pseudoephedrine was preferred to triprolidine alone, pseudoephedrine alone, or placebo.</p> <p>Drowsiness, dry mouth and dizziness were the most commonly reported adverse events.</p> <p>Secondary: Not reported</p>
Urticaria				
<p>Jolliffe et al.³⁵ (1985)</p> <p>Brompheniramine SR 12 mg BID for 4 weeks</p> <p>vs</p> <p>clemastine 1 mg BID for 4 weeks</p> <p>vs</p> <p>placebo for 4 weeks</p>	<p>PC, XO</p> <p>Patients 18 to 62 years of age with chronic urticaria (with or without dermatographism)</p>	<p>N=24</p> <p>12 weeks</p>	<p>Primary: Symptom severity and degree of improvement</p> <p>Secondary: Not reported</p>	<p>Primary: Investigators and patients found that both brompheniramine and clemastine were more effective than placebo with regards to symptom severity.</p> <p>In those patients who expressed a positive preference for one therapy, more patients preferred brompheniramine treatment to either clemastine (P<0.025) or placebo treatment (P<0.005).</p> <p>Drowsiness was experienced by four patients taking brompheniramine compared to three patients taking clemastine.</p> <p>Secondary: Not reported</p>
<p>Gale et al.³⁶ (1989)</p> <p>Chlorpheniramine 4 mg TID for 24 days</p> <p>vs</p>	<p>DB, RCT, XO</p> <p>Patients >16 years of age with chronic idiopathic urticaria</p>	<p>N=20</p> <p>48 days</p>	<p>Primary: Patients' and physician's assessment of treatment of chronic idiopathic urticaria</p>	<p>Primary: There were no significant differences between acrivastine and chlorpheniramine in relieving itching, wheal, or overall discomfort in the patient assessment (P value not reported).</p> <p>There were no significant differences between acrivastine and chlorpheniramine in itching or wheal in the physician's assessment (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acrivastine 8 mg TID for 24 days			Secondary: Not reported	Secondary: Not reported
Upper Respiratory Conditions				
Bye et al. ³⁷ (1980) Triprolidine 2.5 mg and pseudoephedrine 60 mg 1 tablet TID vs triprolidine 2.5 mg 1 tablet TID vs pseudoephedrine 60 mg 1 tablet TID vs placebo Tablets were taken for as long as needed.	DB, PC, RCT Adults with symptoms of the common cold	N=466 (243 colds) 8 to 10 days	Primary: Symptoms (daily diary card), adverse events, overall impression of improvement Secondary: Not reported	Primary: The sneezing score was reduced with triprolidine/pseudoephedrine compared to placebo on days two, three and four of the cold (P<0.01). Sneezing was also reduced by pseudoephedrine on days two and three compared to placebo (P<0.01). Nasal obstruction was improved with pseudoephedrine and triprolidine/pseudoephedrine on day one only (P<0.01). The other specific symptoms were not significantly affected by the treatments. Difficulty in sleeping was significantly higher for patients taking pseudoephedrine compared to placebo. Significantly more patients receiving pseudoephedrine and triprolidine/pseudoephedrine reported “improvement” improved in symptoms compared to placebo (P<0.01). Secondary: Not reported
Central Nervous System Adverse Effects				
Seppälä et al. ³⁸ (1981) Brompheniramine 12 mg for 3 doses	DB, RCT, XO Healthy men 20 to 25 years of age	N=9 5 weeks	Primary: Psychomotor performance, subjective assessments, sleep estimates	Primary: No significant drug effects were seen on divided attention, tracking or on the speed anticipation test. The reaction times quickened during the study (P<0.01). The reactions of the subjects were slower (P<0.05 vs placebo) two hours after the first dose

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>carbinoxamine 12 mg for 3 doses</p> <p>vs</p> <p>clemastine 1.34 mg for 3 doses</p> <p>vs</p> <p>phenylpropranolamine 50 mg for 3 doses</p> <p>vs</p> <p>placebo</p> <p>Doses were administered at 8:30 AM and 9:00 PM on the first day, and at 8:30 AM on the following day.</p>			<p>Secondary: Not reported</p>	<p>of carbinoxamine on day one, but reactions returned to normal thereafter. Phenylpropranolamine improved reaction times (P<0.05) compared to placebo, carbinoxamine and brompheniramine.</p> <p>Clemastine and brompheniramine slightly decreased and phenylpropranolamine significantly decreased (P<0.001) reaction mistakes compared to placebo.</p> <p>On both treatment days, phenylpropranolamine enhanced the ability to distinguish between two discrete flashes of light. The effect was significant in comparison with placebo, carbinoxamine and brompheniramine (P<0.01).</p> <p>No treatment significantly affected the subjective feeling of performance. On the first day of treatment, antihistamines were estimated to be a tranquilizer more often than placebo, but only clemastine differed significantly from placebo (P<0.05). On day two, no active treatment differed from placebo.</p> <p>Diurnal variation in the alertness-drowsiness scale was seen during placebo administration. Antihistamines tended to cause drowsiness. Significant differences in drowsiness were seen with brompheniramine (six hours after dose) and clemastine (12 hours after dose) compared to placebo. Drowsiness was felt only on the first day of antihistamine treatment. Phenylpropranolamine increased alertness.</p> <p>Secondary: Not reported</p>
<p>Nicholson et al.³⁹ (1979)</p> <p>Brompheniramine 4 mg IR as a single dose</p> <p>vs</p>	<p>DB, PC, RCT, XO</p> <p>Healthy volunteers</p>	<p>N=6</p> <p>>4 weeks</p>	<p>Primary: Visuomotor coordination and subjective assessments of performance, well-being and sleep</p> <p>Secondary:</p>	<p>Primary: Brompheniramine IR (4 mg) impaired performance at 1.5 hours and 3.0 hours (P<0.05). Brompheniramine SR (12 mg) impaired performance at 1.5 hours (P<0.001).</p> <p>Triprolidine IR (2.5 mg) had an immediate effect on performance (P<0.001) which persisted for 3.0 hours (P<0.01). Triprolidine SR (10 mg) impaired performance from 1.5 hours (P<0.001) to 5.0 hours (P<0.01).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
brompheniramine 12 mg SR as a single dose vs triprolidine 2.5 mg IR as a single dose vs triprolidine 10 mg SR as a single dose vs placebo			Not reported	Performance reached placebo level about seven hours after triprolidine (2.5 and 10 mg), and about five hours after brompheniramine (4 and 12 mg). There were no consistent changes in the assessments of well-being, sleep and performance among any of the antihistamines compared to placebo. Secondary: Not reported
Ng et al. ⁴⁰ (2004) Chlorpheniramine 4 mg as a single dose vs cetirizine 10 mg as a single dose vs placebo	DB, PC, RCT, XO Children 7 to 14 years of age with allergic rhinitis	N=24 >3 weeks	Primary: P300 event-related potential (objective measure of sedation) and sleepiness or somnia using a VAS (subjective measure of sedation) Secondary: Not reported	Primary: There was an increase in P300 latency for chlorpheniramine (P=0.04) and cetirizine (P=0.03) compared to baseline, but this was not demonstrated with placebo. However, the mean percentage change in P300 latency for cetirizine and chlorpheniramine did not differ significantly from placebo. There was no significant increase in VAS scores for chlorpheniramine, cetirizine or placebo compared to baseline (P>0.05). The mean percentage change in VAS scores for cetirizine and chlorpheniramine did not differ significantly from placebo. Secondary: Not reported
Kamei et al. ⁴¹ (2003) Chlorpheniramine 4 mg as a single	DB, PC, RCT, XO Healthy volunteers	N=11 4 weeks	Primary: CFF, CRT, CTT, RVIP, LARS, WA Secondary:	Primary: There was no significant difference in CFF or CRT among the treatment groups. Chlorpheniramine significantly reduced the tracking ability in the CTT

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose vs fexofenadine 120 mg as a single dose vs olopatadine 10 mg as a single dose vs placebo			Not reported	compared to placebo (P<0.01). There was no significant difference in RVIP among the treatment groups. There was no significant difference in LARS among the treatment groups. In the WA analysis, chlorpheniramine and olopatadine caused a significant reduction in behavioral activity compared to placebo (P<0.05 and P<0.01, respectively). There was also a significant difference between fexofenadine and olopatadine groups (P<0.01). Secondary: Not reported
Hindmarch et al. ⁴² (1976) Clemastine 1.34 mg BID for 3 days vs placebo	DB, PC, XO Healthy volunteers	N=21 11 days	Primary: Car driving ability, personality and subjective feeling states Secondary: Not reported	Primary: There was no significant difference in car driving ability (garaging a car, controlled braking ability, estimation of width at a distance, maneuvering ability, reverse parking) with clemastine compared to placebo. There was no significant difference in the Middlesex Hospital Questionnaire between clemastine and placebo, which assessed personality and subjective feeling states. Secondary: Not reported
Cohen et al. ⁴³ (1987) <u>Study 1</u> Diphenhydramine 50 mg vs diphenhydramine	DB, PC, XO Healthy volunteers	<u>Study 1</u> N=12 Single dose <u>Study 2</u> N=12 Single dose	Primary: Adaptive tracking test, reaction time, body sway, eye movement tests (Study 1) Secondary: Not reported	Primary: <i>Study 1</i> Alcohol alone and acrivastine alone produced no impairment in tracking performance at any time during the study. Diphenhydramine alone (50 mg) reduced tracking performance at 2.5 hours after drug administration compared to placebo. At one hour, the effects of diphenhydramine plus alcohol were significantly different from placebo, but not from alcohol alone. At 2.5 hours, diphenhydramine plus alcohol (50 mg) caused impairment of performance compared to all other treatment groups. Acrivastine plus alcohol (8 mg) impaired tracking at 2.5 hours compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
50 mg and alcohol 32 mL vs acrivastine 8 mg vs acrivastine 8 mg and alcohol 32 mL vs alcohol 32 mL vs placebo <u>Study 2</u> Acrivastine 4 mg and alcohol 32 mL vs acrivastine 8 mg and alcohol 32 mL vs terfenadine† 60 mg and alcohol 32 mL vs terfenadine† 120				<p>with placebo and single treatments, but produced significantly less impairment than diphenhydramine plus alcohol (50 mg).</p> <p>No single treatment prolonged reaction time at any time, with the exception of alcohol alone. It significantly increased reaction time compared to placebo at one hour. At one hour, diphenhydramine plus alcohol (50 mg) increased reaction time compared to placebo and all other treatments. At 2.5 hours, diphenhydramine plus alcohol (50 mg) was different from all of the single treatments (including placebo), but did not differ from the acrivastine and alcohol (8 mg) combination. The acrivastine plus alcohol (8 mg) differed from placebo and acrivastine alone at one hour, but not from alcohol alone. At 2.5 hours, acrivastine plus alcohol (8 mg) prolonged reaction time compared with placebo, alcohol and acrivastine alone.</p> <p>With regards to body sway, the main effects occurred at one hour. Impairment after the diphenhydramine plus alcohol (50 mg) combination was significantly different from all single treatments (excluding diphenhydramine alone). The acrivastine plus alcohol (8 mg) combination differed from placebo, alcohol alone and acrivastine alone.</p> <p>The eye movement analyses included smooth pursuit velocity, as well as PSV duration and reaction time. Diphenhydramine plus alcohol (50 mg) impaired PSV compared with placebo and alcohol at 1 and 2.5 hour(s). At 2.5 and 7.5 hours, PSV was also decreased by diphenhydramine alone (50 mg). No significant differences were seen after acrivastine (8 mg) or alcohol, either alone or in combination. The duration of the saccades of 30° showed similar effects to the PSV. Diphenhydramine plus alcohol (50 mg) was different from placebo, alcohol alone, and acrivastine alone (8 mg) at one hour and from all the other treatments at 2.5 hours. At 2.5 hours, diphenhydramine alone (50 mg) was different from placebo. Both acrivastine (8 mg) and alcohol alone produced no effects, but their combination increased the duration of saccade at 1 and 2.5 hour(s) compared with placebo, but not with alcohol alone. Diphenhydramine alone (50 mg) and the combination with alcohol produced prolongation in the duration of saccade at 1 and 2.5 hour(s) compared with placebo. At 2.5 hours, diphenhydramine plus alcohol (50 mg) also produced significant</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>mg and alcohol 32 mL</p> <p>vs</p> <p>alcohol 32 mL</p> <p>vs</p> <p>placebo</p>				<p>impairment compared to alcohol alone. None of the other single treatments produced impairment compared with placebo. Acrivastine plus alcohol (8 mg) impaired reaction time at 1 and 2.5 hour(s) compared with placebo, but not with alcohol. Smooth pursuit velocity was significantly reduced after alcohol and acrivastine plus alcohol (8 mg) compared with placebo, but acrivastine plus alcohol (8 mg) was not different from alcohol alone. There were no differences between placebo and any of the other treatments.</p> <p><i>Study 2</i> At 1 hour, alcohol alone and all drug/alcohol combinations prolonged reaction time and there were no differences between the combination treatments and alcohol alone. At 2.5 hours, the combination treatments had prolonged reaction time compared with placebo, but alcohol did not. There were no differences between alcohol-containing treatments and alcohol alone.</p> <p>With regards to body sway, at 1 and 2.5 hour(s), all drug/alcohol combinations and alcohol alone differed significantly from placebo. However, there was no difference between any of the active treatments.</p> <p>Secondary: Not reported</p>
<p>Ramaekers et al.⁴⁴ (1994)</p> <p>Diphenhydramine-50 mg as a single dose</p> <p>vs</p> <p>acrivastine 8 mg as a single dose</p> <p>vs</p>	<p>DB, RCT, XO</p> <p>Healthy female volunteers 21 to 45 years of age</p>	<p>N=18</p> <p>10 to 11 weeks</p>	<p>Primary: Two repetitions of the highway driving test and car-following test given 1.5 to 2.75 hours (first trial) and 3.25 to 4.50 hours (second trial) post dosing</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Highway Driving</i> All acrivastine doses significantly impaired driving (P<0.05) in the first trial. Only the 24 mg dose remained significant in the second trial (P=0.014). The combination of acrivastine (8 mg) with pseudoephedrine (60 mg) had no significant effect on highway driving in either trial. There was no significant effect of any terfenadine dose in either trial. Diphenhydramine significantly impaired driving in both trials (P=0.000 and 0.001, respectively).</p> <p>The effect of diphenhydramine differed from all other treatments in both trials, except acrivastine 16 and 24 mg. In the first trial, the effect of 16 mg acrivastine differed significantly from that of all three terfenadine doses. In the second trial, the effect of 24 mg acrivastine differed</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acrivastine 16 mg as a single dose vs acrivastine 24 mg as a single dose vs acrivastine 8 mg and pseudoephedrine 60 mg as a single dose vs terfenadine 60 mg as a single dose vs terfenadine 120 mg as a single dose vs terfenadine 180 mg as a single dose vs placebo				<p>significantly from that of terfenadine (120 and 60 mg). No other pair of treatment effects differed significantly.</p> <p>The difference in driving impairment was significant between placebo and diphenhydramine in both trials (P=0.010 and P=0.020, respectively); between placebo and acrivastine (16 mg) and terfenadine (60 mg) in the first trial (P=0.001 and P=0.031, respectively); between placebo and acrivastine (24 mg) in the second trial (P=0.018). The combination of acrivastine and pseudoephedrine had no significant effect on driving impairment compared to placebo.</p> <p><i>Car-Following Test</i> The combined effect of all acrivastine doses on reaction time was significant in the first trial (P=0.046). The effects were also significant specifically for the 16 mg dose (P=0.027) and the 24 mg dose (P=0.04) compared to placebo. The effect of 24 mg dose remained significant in the second trial (P=0.025). The combination of acrivastine with pseudoephedrine had no significant effect on reaction time in either trial compared to placebo. There was no significant effect of any terfenadine dose (or combination of doses) in either trial. Diphenhydramine significantly affected reaction time in both trials (P=0.000 and P=0.042, respectively).</p> <p>Secondary: Not reported</p>
Vuurman et al. ⁴⁵ (1996)	DB, PG, RCT Atopic subjects 16	N=104 14 days	Primary: Symptom scores, memory test,	Primary: There were significant improvements in symptoms on day 1 with diphenhydramine and acrivastine plus pseudoephedrine compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Diphenhydramine 50 mg QD</p> <p>vs</p> <p>acrivastine 8 mg and pseudoephedrine 60 mg QD administered as a fixed-dose combination</p> <p>vs</p> <p>placebo</p>	<p>to 25 years of age with seasonal allergic rhinitis requiring antihistamine therapy and matched controls who did not require antihistamine therapy</p>		<p>learning test, examination performance</p> <p>Secondary: Not reported</p>	<p>placebo (P=0.024 and P=0.029, respectively). There were no significant treatment effects on day two or day three. At examination, symptom scores were not significantly different between groups.</p> <p>There was no overall treatment effects regarding the number of words during immediate recall (P=0.761); however, there was a significant increase over time in overall performance (P<0.001). Analysis of the scores for each day showed no significant differences between the groups on any day. There was no overall effect of treatment found on any day, or over all days, in mean delayed recall results; however, there was a significant increase over time (P<0.001).</p> <p>Training and examination scores increased in all groups. Atopic subjects had significantly lower scores than the control group (P=0.043). There was a significant performance deficiency noted after administration of diphenhydramine in atopic subjects compared to controls (P<0.001). Performance after acrivastine plus pseudoephedrine was significantly better than after administration of diphenhydramine (P=0.001). The difference between placebo and diphenhydramine was not significant (P=0.067). Performance after acrivastine plus pseudoephedrine was not significantly different from placebo (P=0.13) or controls (P=0.87).</p> <p>Atopic subjects performed significantly worse than controls in the performance at examination analysis (P=0.012). There was a significant performance deficiency noted after administration of diphenhydramine in atopic subjects compared to controls (P<0.001). The mean performance after acrivastine plus pseudoephedrine was significantly better than after administration of diphenhydramine (P=0.001). Performance after acrivastine plus pseudoephedrine was not significantly different from the control group (P=0.73).</p> <p>Secondary: Not reported</p>
<p>Simons et al.⁴⁶ (1996)</p> <p>Diphenhydramine</p>	<p>DB, PC, RCT, XO</p> <p>Healthy men 18 to 40 years of age</p>	<p>N=15</p> <p>>7 weeks</p>	<p>Primary: Cognitive function assessed using the P300-event-related</p>	<p>Primary: The percent change in the P300 latency from baseline from least to greatest was: terfenadine, placebo, cetirizine, ketotifen, loratadine, astemizole and diphenhydramine. Diphenhydramine increased the P300</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
50 mg as a single dose vs astemizole 10 mg as a single dose vs cetirizine 10 mg as a single dose vs ketotifen 2 mg as a single dose vs loratadine 10 mg as a single dose vs terfenadine† 60mg as a single dose vs placebo			potential, and subjective assessment of somnolence using a VAS Secondary: Not reported	latency significantly compared with baseline and with placebo. The mean change in the visual analogue scale for somnolence from least to greatest was: placebo, astemizole, terfenadine, loratadine, cetirizine, ketotifen and diphenhydramine. Somnolence was significantly greater than baseline after astemizole, terfenadine and loratadine. It was also significantly greater than baseline and placebo after cetirizine, ketotifen and diphenhydramine. The effect of terfenadine, cetirizine, ketotifen, loratadine, and astemizole on the P300 latency and the visual analogue scale did not differ significantly from that of diphenhydramine. Secondary: Not reported
Schweitzer et al. ⁴⁷ (1994) Diphenhydramine 50 mg TID for 3 consecutive days	DB, RCT, XO Healthy atopic adults	N=12 >28 days	Primary: MSLT, SALT, VAS sleepiness ratings, global sleepiness and performance	Primary: <i>MSLT</i> Mean sleep latencies were 7.5, 5.5, and 7.8 minutes on day one for cetirizine, diphenhydramine, and placebo, respectively, and 8.0, 8.3, and 8.3 minutes on day three.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cetirizine 10 mg for 3 consecutive days QD vs placebo			ratings Secondary: Not reported	<p>On day one, diphenhydramine produced significant sedation at 1:00 PM and 5:00 PM relative to placebo (P<0.05) and at 11:00 AM (P=0.056) and 1:00 PM (P<0.05) compared with cetirizine. There were no differences between placebo and cetirizine on treatment day 1 and no differences among the three conditions on treatment day three.</p> <p>There was a significant decrease in physiologic sleepiness with diphenhydramine on day three compared with day one (P<0.05). During both treatment days, physiologic sleepiness was maximal at 11:00 AM and generally decreased as the day progressed for all conditions.</p> <p><i>SALT</i></p> <p>On day 1, subjects made fewer correct responses with diphenhydramine (83.1%) than with cetirizine (87.8%) or placebo (88.9%; P<0.05 for both). On day 3, correct response rate was equivalent among the three treatment groups.</p> <p>Performance improved on day three (compared with day one) in the diphenhydramine group (P<0.05), whereas performance remained stable on day three in the other two treatment groups. Performance was most impaired on day one during the two morning test periods after diphenhydramine administration and was impaired to a lesser extent in the afternoon after the second diphenhydramine dose.</p> <p>On treatment day one, subjects responded twice as quickly to assembly line malfunctions in the cetirizine and placebo groups (1.3 seconds and 1.2 seconds, respectively) compared with diphenhydramine (2.6 seconds, P<0.05 for both). Response time with diphenhydramine improved on day 3 (1.7 seconds, P<0.05 compared with day one).</p> <p><i>VAS Sleepiness Ratings</i></p> <p>Subjects rated themselves as 20% sleepier with diphenhydramine compared with placebo (P<0.05) and 14% sleepier compared with cetirizine (P=0.08). Subjective ratings of sleepiness did not differ between cetirizine and placebo.</p> <p>Subjects rated themselves as slightly more alert on day three compared</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>with day one. Subjects judged that they were sleepest at 11:00 AM and 3:00 PM. On day one, diphenhydramine produced significantly more subjective sleepiness than placebo at 11:00 AM, 1:00 PM, 3:00 PM, and 5:00 PM (P<0.05).</p> <p><i>Global Sleepiness and Performance Ratings</i> Subjects rated themselves as being more sleepy at the end of diphenhydramine treatment on day one compared with cetirizine and placebo (P<0.05 for both), which did not differ from each other. On treatment day three, there were no significant differences among the three groups.</p> <p>Subjects rated themselves as being significantly more alert at the end of day three in the diphenhydramine condition compared with treatment day one (P<0.001), whereas alertness ratings were similar on both treatment days for cetirizine and placebo.</p> <p>Performance was poorer on day one with diphenhydramine compared with cetirizine (P<0.01) and placebo (P=0.083), which did not differ from each other. Performance ratings improved on day 3 with diphenhydramine compared to day one (P<0.01). Performance ratings during the cetirizine and placebo conditions were similar on both treatment days. There were no significant differences among the three groups on day three.</p> <p>Secondary: Not reported</p>
<p>Simons et al.⁴⁸ (1999)</p> <p>Diphenhydramine 50 mg as a single dose</p> <p>vs</p> <p>chlorpheniramine 8 mg as a single</p>	<p>DB, PC, RCT, XO</p> <p>Healthy subjects >65 years of age</p>	<p>N=15</p> <p>>5 weeks</p>	<p>Primary: Cognitive function assessed using the P300-event-related potential, and subjective assessment of somnolence using a VAS</p> <p>Secondary:</p>	<p>Primary: The change in the P300 latency from baseline from least to greatest was: cetirizine, placebo, loratadine, diphenhydramine, and chlorpheniramine. However, there were no significant differences in the in P300 latency measurements at 2 to 2.5 hours after dosing compared to predose values (P>0.05).</p> <p>The change in VAS for somnolence from least to greatest was: placebo, loratadine, cetirizine, chlorpheniramine, and diphenhydramine. There were no significant differences in the subjective assessment of somnolence 2 to 2.5 hours after dosing compared to predose values (P>0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose vs cetirizine 10 mg as a single dose vs loratadine 10 mg as a single dose vs placebo			Not reported	Secondary: Not reported
Vuurman et al. ⁴⁹ (2004) Diphenhydramine 50 mg as a single dose vs desloratadine 5 mg as a single dose vs placebo	AC, DB, PC, RCT, XO Healthy volunteers	N=18 >3 weeks	Primary: Driving performance (SDLP) and psychomotor performance Secondary: Not reported	Primary: In the highway driving test, significantly more weaving behavior occurred following treatment with diphenhydramine (P<0.001 vs desloratadine or placebo). The mean SDLP was comparable following treatment with desloratadine or placebo. Subjects maintained a more constant speed with desloratadine than with diphenhydramine treatment (P=0.045); there was no significant difference between desloratadine and placebo. In the car-following test, mean brake reaction time was significantly shorter with desloratadine than with placebo (P=0.033) or diphenhydramine (P=0.001). No significant difference was observed between the diphenhydramine and placebo groups. No significant differences were observed among the groups with regard to headway variability. Subjects treated with diphenhydramine demonstrated a significantly greater increase in sleepiness score from baseline compared with desloratadine (P<0.001) or placebo (P<0.001). No difference was observed between the desloratadine and placebo groups. Mean tracking error significantly increased from baseline following treatment with diphenhydramine compared with desloratadine and placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>(P=0.002 and P=0.001, respectively). Diphenhydramine significantly increased mean reaction time compared with desloratadine (P=0.014). There was no significant difference between desloratadine and placebo for either of these parameters.</p> <p>Secondary: Not reported</p>
<p>Wilken et al.⁵⁰ (2003)</p> <p>Diphenhydramine 50 mg as a single dose</p> <p>vs</p> <p>desloratadine 5 mg as a single dose</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, PG, RCT</p> <p>Healthy adults 18 to 60 years of age with ragweed induced allergic rhinitis</p>	<p>N=248</p> <p>1 week</p>	<p>Primary: Vigilance and cognitive performance battery; symptom evaluation</p> <p>Secondary: Not reported</p>	<p>Primary: Subjects taking diphenhydramine performed significantly worse on all parameters of vigilance compared with subjects taking either desloratadine or placebo.</p> <p>Subjects taking diphenhydramine performed significantly worse on measures across other cognitive domains (working memory, psychomotor speed, reasoning/computation, divided attention) compared with subjects taking either desloratadine or placebo. There were no statistically significant differences between subjects taking placebo and those taking desloratadine on any of the measures of cognitive functioning.</p> <p>Subjects taking diphenhydramine reported significantly worse functioning on the performance battery (P<0.001) compared with subjects taking desloratadine or placebo. Subjects in the diphenhydramine group reported a significantly greater degree of sedation (P<0.001) following the completion of the Stanford Sleepiness Scale test battery than subjects taking either desloratadine or placebo. Subjects taking diphenhydramine reported being significantly drowsier, more lethargic, and less clear-headed, quick-witted, attentive, coordinated, and proficient than subjects taking desloratadine or placebo. Subjects in the desloratadine group reported being significantly more clear-headed (P=0.05) and less drowsy (P=0.046) than those in the placebo group.</p> <p>Desloratadine and diphenhydramine treatment led to significant reductions in TTSSs (P<0.001 and P<0.04, respectively) and TNSSs (P<0.001 and P<0.046, respectively) compared to placebo. There was a significant improvement in nonnasal symptoms for subjects taking diphenhydramine (P<0.001) compared with subjects taking placebo; however, this finding was not significant for desloratadine. Self-reported global therapeutic</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>response was significantly better in subjects taking either desloratadine (P=0.03) or diphenhydramine (P<0.001) compared with placebo.</p> <p>Secondary: Not reported</p>
<p>Mansfield et al.⁵¹ (2003)</p> <p>Diphenhydramine 50 mg as a single dose</p> <p>vs</p> <p>fexofenadine 180 mg as a single dose</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT, XO</p> <p>Healthy volunteers</p>	<p>N=44</p> <p><40 days</p>	<p>Primary: Cognitive performance using the Test of Variables of Attention</p> <p>Secondary: Not reported</p>	<p>Primary: Mean response time was significantly longer with diphenhydramine than with placebo (P=0.0230). There was no significant difference between fexofenadine and placebo (P=0.5264), nor was there a significant difference between fexofenadine and diphenhydramine (P=0.1258).</p> <p>There was a significant difference in the average omission error values between diphenhydramine and placebo (P=0.0398). Fexofenadine and placebo were not statistically different (P=0.6389) nor was fexofenadine and diphenhydramine (P=0.1028).</p> <p>The frequency of commission errors was not significantly different for diphenhydramine or fexofenadine compared to placebo (P=0.4975 and P=0.1483, respectively). However, diphenhydramine was associated with significantly more commission errors than fexofenadine (P=0.0354).</p> <p>Diphenhydramine was associated with significantly more drowsiness than placebo (P=0.0004). Fexofenadine was not statistically different from placebo for drowsiness scores (P=0.0810). There was no significant difference in drowsiness with diphenhydramine compared to fexofenadine (P=0.0742).</p> <p>Secondary: Not reported</p>
<p>Weiler et al.⁵² (2000)</p> <p>Diphenhydramine 50 mg as a single dose</p> <p>vs</p>	<p>DB, RCT, XO</p> <p>Licensed drivers with seasonal allergic rhinitis</p>	<p>N=41</p> <p>4 weeks</p>	<p>Primary: Driving performance (using the Iowa Driving Simulator) and self-reported drowsiness</p>	<p>Primary: <i>Phase 1</i></p> <p>After taking diphenhydramine, participants performed car-following with significantly less coherence than after taking alcohol, fexofenadine, or placebo (95% CI excludes zero).</p> <p>Significant differences in minimum following distance were observed among the four treatments. When participants performed car-following</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>fexofenadine 60 mg as a single dose</p> <p>vs</p> <p>alcohol (~0.1% blood alcohol concentration)</p> <p>vs</p> <p>placebo</p>			<p>Secondary: Not reported</p>	<p>after consuming alcohol, they had significantly smaller minimum following distances than they did after taking fexofenadine or placebo. There was no significant difference in car-following after taking diphenhydramine and alcohol.</p> <p>After participants took fexofenadine, they had significantly less steering instability than after taking diphenhydramine or alcohol, but not placebo. After participants took placebo, they had significantly less steering instability than after consuming alcohol or diphenhydramine.</p> <p><i>Phase 2</i> After completing phase 1, participants drove the remaining 30 miles of the course "as you normally would drive."</p> <p>After participants took fexofenadine, they had significantly less steering instability than after taking diphenhydramine or alcohol, but not placebo. After participants took placebo, they had significantly less steering instability than after consuming alcohol or diphenhydramine. After participants consumed alcohol, they had the same or less steering instability than after taking diphenhydramine.</p> <p>No significant differences for lane excursions to the right were noted among the four treatments. Significant differences were noted the four treatments for excursions to the left. After participants took diphenhydramine, they crossed the center line significantly more often than after taking fexofenadine or placebo. After participants took alcohol, they crossed the center line significantly more often than after taking fexofenadine and placebos. Fexofenadine and placebo did not differ significantly.</p> <p>There were no significant differences among the treatment groups on response time to a blocking vehicle. However, after consuming alcohol, participants responded more slowly to the event than after they took fexofenadine. Responses to the blocking vehicle were categorized as clear avoidance, potentially unsafe avoidance, or collision. The overall differences were not significant.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Drowsiness scores on the second visual analogue scale (given 1 hour after treatment administration) were not significantly different among the treatment groups. At the time of the third visual analogue scale (just before the drive), participants were significantly more drowsy after taking diphenhydramine and least drowsy after taking fexofenadine or placebo. The differences between diphenhydramine and fexofenadine or placebo were significant. After the drive, participants were most drowsy with diphenhydramine and least drowsy with placebo. The difference between fexofenadine and placebo was not significant. Participants reported significantly higher levels of drowsiness with diphenhydramine than with fexofenadine and placebo.</p> <p>Secondary: Not reported</p>
<p>Gandon et al.⁵³ (2002)</p> <p>Diphenhydramine 50 mg QD for 5 consecutive days</p> <p>vs</p> <p>levocetirizine 5 mg QD for 5 consecutive days</p> <p>vs</p> <p>placebo</p>	<p>XO</p> <p>Healthy volunteers</p>	<p>N=19</p> <p>>1 month</p>	<p>Primary: CFF</p> <p>Secondary: CRT, body sway, LMT, and subjective assessments of alertness</p>	<p>Primary: The mean CFF values for levocetirizine and placebo were not significantly different from each other globally across all time points (P=0.292) or at any specific time point. Mean CFF values after diphenhydramine administration was significantly different than placebo across all time points (P=0.019) and at one, two and three hours after dosing (P<0.04).</p> <p>Secondary: Mean CRT scores were comparable over time for the three treatments, with no significant differences for groups on day five.</p> <p>With regards to body sway, results on distance and surface displacement from the center of gravity (measured with eyes open or closed) were similar for levocetirizine and placebo. An increase in total displacement distance was demonstrated up to three hours after dosing with diphenhydramine on day one (eyes closed: 16.35 cm (95% CI, 5.61 to 27.10).</p> <p>Scores of alertness increased after levocetirizine and placebo. A decrease in alertness was observed after diphenhydramine administration on day one compared with placebo.</p> <p>There was a similar evolution of contentedness in all three treatments on</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>days one and five. There was no consistent decrease in calmness observed with any treatment. There was no significant difference in LMT among the three treatment groups.</p>
<p>Verster et al.⁵⁴ (2003)</p> <p>Diphenhydramine 50 mg as a single dose on 4 consecutive days</p> <p>vs</p> <p>levocetirizine 5 mg as a single dose on 4 consecutive days</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT, XO</p> <p>Healthy volunteers</p>	<p>N=48</p> <p>>3 weeks</p>	<p>Primary: Memory, psychomotor performance, mood</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>On the word learning test, learning was not significantly impaired after administration of either levocetirizine or diphenhydramine compared to placebo on day one or day four.</p> <p>On the Sternberg Memory Scanning Test, there were no significant differences in reaction time or percentage of errors made during test performance between the treatments and placebo on day one. On day four, there were no significant differences on memory-scanning parameters between the treatments and placebo.</p> <p>On the tracking test, tracking ability after administration of diphenhydramine was significantly impaired in both the easy and hard versions of the test on day one (P<0.0001 for both). Tracking ability after administration of levocetirizine was not significantly impaired compared to placebo. On day four, there were no significant differences between the treatments and placebo.</p> <p>On the divided attention test, tracking ability after administration of diphenhydramine was significantly different from that after placebo on day one (P<0.0001). Tracking ability after administration of levocetirizine was not significantly different from that after placebo. Compared to placebo, reaction times after administration of diphenhydramine were significantly increased (P<0.0001). Reaction times with levocetirizine did not change. On day four, there were no significant differences between treatments and placebo on divided attention test parameters.</p> <p>After administration of diphenhydramine, scores on the ARCI-49 questionnaire indicated significantly increased sedation on days one and four. Euphoria, intellectual efficacy and energy were significantly decreased with diphenhydramine. The effects of levocetirizine on all ARCI-49 scales were not significantly different from the effects of placebo.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Verster et al. ⁵⁵ (2003) Diphenhydramine 50 mg as a single dose on 4 consecutive days vs levocetirizine 5 mg as a single dose on 4 consecutive days vs placebo	DB, PC, RCT, XO Healthy volunteers	N=48 >3 weeks	Primary: Driving performance (SDLP) and subjective assessments Secondary: Not reported	Primary: When assessing the acute effects of treatment, the majority of individual SDLPs after levocetirizine were similar to placebo (P=not significant). Only 16.7% of subjects drove worse than the acceptance limit. For those receiving diphenhydramine, 43.8% drove worse than the legal limit (for driving in The Netherlands; P<0.0001). The SDLP of diphenhydramine differed significantly from placebo (P<0.0001). No significant effects were found for the other parameters of the driving test. When assessing the sub-chronic effects of treatment, the majority of individual SDLPs after levocetirizine were similar to placebo (P=not significant). Only 16.7% of subjects drove worse than the acceptance limit. For those receiving diphenhydramine, 31.1% of subjects drove worse than the legal limit (for driving in The Netherlands; P<0.001). The SDLP of diphenhydramine differed significantly from placebo (P<0.0003). No significant effects were found for the other parameters of the driving test. In the subjective assessment (acute treatment), diphenhydramine significantly reduced driving quality (P<0.0001), increased mental effort during driving (P<0.0001), and reduced alertness (P<0.0001). There were no significant differences found between levocetirizine and placebo. In the subjective assessment (sub-chronic treatment), driving quality and mental effort during driving did not differ significantly between the treatments. Alertness was significantly reduced after diphenhydramine compared to placebo (P<0.005). The level of alertness did not differ between levocetirizine and placebo. Secondary: Not reported
Bender et al. ⁵⁶ (2001) Diphenhydramine	DB, PC, PG, RCT Children 8 to 10 years of age with	N=63 15 days (4 laboratory	Primary: Total Verbal Instruction Score, Total Reading	Primary: In the Verbal Instruction Score, no significant treatment-group differences were found. Errors decreased significantly with age (P<0.0001) and over time (P<0.0001) as familiarity with materials and testing situations

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>25 mg twice daily (6 hours apart) on 3 different school days</p> <p>vs</p> <p>loratadine 10 mg QD on 3 different days</p> <p>vs</p> <p>placebo</p>	<p>allergic rhinitis requiring an antihistamine</p>	<p>school days)</p>	<p>Recall Score, Total Average Reaction Time, and Somnolence Scale using a computer-administered neuropsychologic test battery (administered on four school days)</p> <p>Secondary: Not reported</p>	<p>increased.</p> <p>In the Reading Test Score, no significant treatment-group differences were found. Both age and baseline reading ability were significant covariates ($P<0.0001$), and errors decreased markedly over time ($P<0.0001$).</p> <p>For Average Reaction Time, no treatment-group differences were found for reaction time or performance scores on any of the four visits. Average reaction time to computer tasks decreased over all four visits ($P<0.0001$).</p> <p>For Somnolence Scale ratings, there was no significant differences between treatment groups ($P=0.17$).</p> <p>Secondary: Not reported</p>
<p>Kay et al.⁵⁷ (1997)</p> <p>Diphenhydramine 50 mg for 1 dose on day 1, then 25 mg QID</p> <p>vs</p> <p>loratadine 10 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, RCT</p> <p>Healthy volunteers</p>	<p>N=98</p> <p>5 days</p>	<p>Primary: Cognitive and psychomotor test performance on day one, day three, and day five, as well as self-reported measures</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Day 1</i></p> <p>Subjects receiving diphenhydramine performed poorly compared with subjects receiving loratadine or placebo on measures of divided attention, working memory, and vigilance. Compared to placebo, loratadine did not adversely affect performance on any of these measures.</p> <p>Subjects receiving diphenhydramine demonstrated poorer performance on a measure of tracking accuracy under divided attention conditions (Cog Screen Dual Task Test) compared with subjects taking loratadine or placebo. Subjects taking loratadine outperformed subjects taking placebo ($P=0.02$).</p> <p>Subjects taking diphenhydramine were less efficient in their performance on the Complex Cognitive Assessment Battery Mark Numbers Test than subjects taking loratadine ($P=0.002$).</p> <p>Subjects taking diphenhydramine obtained lower accuracy scores on the ANAM Running Memory Test compared with subjects taking loratadine ($P=0.008$). ANAM Math throughput scores were also lower for subjects taking diphenhydramine ($P<0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>The CogScreen Shifting Attention Test-Instruction Condition throughput score was higher for subjects who received loratadine (P<0.05) than for subjects taking diphenhydramine.</p> <p>On the Kay Continuous Performance Test, subjects taking diphenhydramine were more likely to make errors of commission and errors of omission (P=0.05 and P=0.002, respectively).</p> <p>Ratings of sleepiness on the Stanford Sleepiness Scale were higher after diphenhydramine than after administration of loratadine (P=0.02). Subjects receiving diphenhydramine reported higher levels of fatigue than subjects receiving loratadine (P<0.001). Subjects receiving diphenhydramine also had lower levels of motivation (P<0.001) and rated the quality of their test performance as lower (P<0.001), compared with subjects receiving loratadine.</p> <p><i>Days three and five</i> There were no differences among the treatment groups for the cognitive and psychomotor tests performed on days three and five. However, subjects who received diphenhydramine performed less well than subjects who received placebo on days three and five on a test of tracking errors. There were no differences between loratadine and placebo on the cognitive and psychomotor tests on day five.</p> <p>Subjects who received diphenhydramine reported greater fatigue (P=0.001) and rated the quality of their test performance as lower (P=0.007) compared with subjects who received loratadine. Subjects in the diphenhydramine group also reported lower motivation than subjects taking loratadine (P=0.001). Loratadine did not differ significantly from placebo with respect to level of motivation, mood, or self appraised quality of performance on day five.</p> <p>Secondary: Not reported</p>
Vuurman et al. ⁵⁸ (1993)	RCT Children 10 to 12	N=52 14 days	Primary: Factual knowledge scores, conceptual	Primary: For factual knowledge scores, atopic children were significantly less knowledgeable than children in the control group (P<0.01). Paired

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Diphenhydramine 25 mg BID (4 hours apart) for 2 weeks</p> <p>vs</p> <p>loratadine 10 mg QD for 2 weeks</p> <p>vs</p> <p>placebo</p>	<p>years of age with seasonal allergic rhinitis requiring antihistamine therapy and matched controls who did not require antihistamine therapy</p>		<p>knowledge scores, composite learning scores</p> <p>Secondary: Not reported</p>	<p>comparisons of the atopic group with controls showed a significant effect of diphenhydramine (P=0.012).</p> <p>For conceptual knowledge scores, atopic children were significantly less knowledgeable than children in the control group (P=0.001). Paired comparisons of the atopic group with controls showed a significant effect of diphenhydramine (P=0.001).</p> <p>Geometric mean survival years (knowledge application scores) were significantly lower in children receiving antihistamines compared to the control group (P<0.02).</p> <p>The composite learning scores were significantly lower in atopic children compared to the control group (P<0.003). Composite learning scores were also lower in atopic children receiving placebo or diphenhydramine compared to the control group (P=0.007 and P=0.002, respectively).</p> <p>Secondary: Not reported</p>
<p>Roth et al.⁵⁹ (1987)</p> <p>Diphenhydramine 50 mg TID for 2 days</p> <p>vs</p> <p>loratadine 10 mg QD for 2 days</p> <p>vs</p> <p>loratadine 40 mg QD for 2 days</p> <p>vs</p>	<p>DB, RCT, XO</p> <p>Healthy adults 19 to 35 years of age</p>	<p>N=16</p> <p>28 days</p>	<p>Primary: Measures of performance and daytime sleepiness</p> <p>Secondary: Not reported</p>	<p>Primary: The nocturnal polysomnogram did not detect any difference among the treatments on any parameter evaluated, including total sleep time, latency to sleep, number and duration of awakenings after sleep onset, and percentages of various sleep stages.</p> <p>There was a significant reduction (increased sleepiness) in mean latency to sleep (P<0.01) with diphenhydramine compared to placebo (P<.01) and both loratadine doses (P<0.01 and P<0.02). The low loratadine dose did not differ from the placebo dose or from the large loratadine dose. Although the high loratadine dose did not differ from the low loratadine dose, it did differ from the placebo dose (P<0.04).</p> <p>Subjects rated themselves as being sleepier with diphenhydramine.</p> <p>The vigilance and reaction time tasks demonstrated no effect of treatments. On the performance battery at 9:30 A.M., diphenhydramine produced decrements in digit symbol substitution (P<0.05), whereas both</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				loratadine doses had no effects. The afternoon performance battery (1:30 P.M.) demonstrated no effects of the treatments. Secondary: Not reported
<p>Witek et al.⁶⁰ (1995)</p> <p><u>Study 1</u> Diphenhydramine 50 mg as a single dose</p> <p>vs</p> <p>terfenadine† 60 mg as a single dose</p> <p>vs</p> <p>placebo</p> <p><u>Study 2</u> Diphenhydramine 25 mg as a single dose</p> <p>vs</p> <p>diphenhydramine 50 mg as a single dose</p> <p>vs</p> <p>chlorpheniramine 4 mg as a single</p>	<p>DB, PC, RCT, XO</p> <p>Healthy volunteers 18 to 45 years of age</p>	<p><u>Study 1</u> N=18</p> <p>>1 week</p> <p><u>Study 2</u> N=20</p> <p>>1 week</p>	<p>Primary: Subjective assessments and psychomotor performance</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Study 1</i> In the subjective assessments, diphenhydramine-induced sleepiness was significantly greater than that reported after terfenadine or placebo (P<0.05). There was no difference in sleepiness between terfenadine and placebo. In the VAS analysis, subjects receiving diphenhydramine reported significantly higher levels of sleepiness at three and five hours after taking the dose than after taking terfenadine or placebo (P<0.05). No significant differences were noted between terfenadine and placebo. Significant reductions in alertness were reported with diphenhydramine compared to terfenadine or placebo at three hours after dosing (P<0.05). The difference between diphenhydramine and terfenadine was still evident five hours after dosing (P<0.05).</p> <p>CRT significantly increased one and three hours after diphenhydramine compared with terfenadine. Diphenhydramine produced significant increases in reaction time relative to placebo three hours after drug. No significant differences between terfenadine and placebo were found. There were significant impairments with diphenhydramine in tracking ability compared to terfenadine or placebo at one and three hours.</p> <p><i>Study 2</i> In the subjective assessments, all antihistamine treatments resulted in significantly higher scores on the Stanford Sleepiness Scale three hours after dosing than those reported after placebo (P<0.05). Sleepiness scores were significantly higher with diphenhydramine 50 mg than diphenhydramine 25 mg three hours after dosing and significantly higher than chlorpheniramine five hours after dosing. In the VAS analysis, all three antihistamines produced significantly higher sleepiness compared to placebo three hours after drug administration (P<0.05). Significant reductions in alertness were reported with diphenhydramine 50 mg. There were no significant differences among treatments in jitteriness self-</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose vs placebo				assessments. All three antihistamines impaired reaction relative to placebo one and three hours after dosing (P<0.05). Chlorpheniramine resulted in prolonged reaction time seven hours after dosing, which was significantly greater than the response following diphenhydramine 25 mg. Tracking was significantly impaired with diphenhydramine (25 and 50 mg) compared to placebo one hour after dosing. At three hours after dosing, diphenhydramine 25 mg significantly impaired tracking relative to placebo and chlorpheniramine. Secondary: Not reported
Cohen et al. ⁶¹ (1985) Triprolidine 2.5 mg as a single dose vs triprolidine 5 mg as a single dose vs acrivastine 4 mg as a single dose vs acrivastine 8 mg as a single dose vs	DB, PC, XO Healthy volunteers	N=12 1 days	Primary: 10-minute tracking test score, reaction time, subjective effects using a VAS Secondary: Not reported	Primary: Triprolidine (2.5 and 5 mg) decreased the time tracking score at 1.5 hours after drug dosing compared with placebo and all the acrivastine treatments. The mean tracking score continued to be impaired three hours after triprolidine (5 mg). None of the acrivastine treatments caused any significant impairment compared to placebo. Reaction time was increased at 1.5 hours after triprolidine (2.5 and 5 mg) compared with placebo, and at three hours (triprolidine 5 mg). None of the treatments were different from placebo 5 hours after drug dosing. None of the acrivastine treatments caused a significant change in reaction time compared with placebo at any time during the study. Triprolidine (2.5 and 5 mg) made subjects feel drowsy, clumsy, lethargic, mentally slow, dreamy, and bored at 1.5 hours after drug dosing compared to placebo. Triprolidine (5 mg) also made them feel muzzier and more incompetent. No effects were noted after any of the acrivastine doses. Effects were seen 3 hours after triprolidine (5 mg) as the subjects felt clumsy, lethargic, and mentally slow. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acrivastine 16 mg as a single dose vs placebo				

†Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily, QID=four times daily, SR=sustained-release, TID=three times daily

Study design abbreviations: AC=active control, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, XO=cross-over

Miscellaneous abbreviations: ANAM=Automated Neuropsychological Assessment Metrics, ARCI=Addiction Research Center Inventory, CFF=critical flicker fusion, CI=confidence interval, CRT=choice reaction time, CTT=compensatory tracking test, LARS=line analogue rating scale, LMT=learning memory test, MSLT=multiple sleep latency test, NAR=nasal airway resistance, PSV=peak saccade velocity, RVIP=rapid visual information processing, SALT=simulated assembly line task, SDLP=standard deviation of lateral position, TAR=total airflow rates, TNSS=total nasal symptom scores, TSS=total symptom scores, VAS=visual rating scale, WA=wrists actigraphy

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 9. Relative Cost of the First Generation Antihistamines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ethanolamine Derivatives				
Carbinoxamine	liquid, tablet	Arbinoxa ^{®*} , Karbinal ER [®]	\$\$\$\$	\$
Clemastine	syrup, tablet	N/A	N/A	\$\$
Diphenhydramine	elixir, injection	N/A	N/A	\$\$
Propylamine Derivatives				
Phenylephrine and chlorpheniramine	drops	N/A	N/A	-\$\$\$

*Generic is available in at least one dosage form or strength.

N/A=Not available

X. Conclusions

The first generation antihistamines are approved for the treatment of allergic and non-allergic conditions; however, they are primarily used for the management of allergic rhinitis, urticaria, and angioedema. They are available as single entity agents, as well as in combination with other first generation antihistamines and oral decongestants. Many of the products are available in a generic formulation.

There are several organizations that provide recommendations on the use of first generation antihistamines. There are a variety of effective treatment options for allergic rhinitis, including H₁-antihistamines. The second generation antihistamines are preferred over first generation agents because they have a lower tendency to cause sedation, anticholinergic effects, and performance impairment.^{1,11} Due to their pharmacokinetic properties (prolonged half-life and active metabolites), the central nervous system effects cannot be eliminated by administering these agents at bedtime.¹ For the treatment of urticaria, antihistamines are the cornerstone of therapy. Second generation antihistamines are generally preferred; however, first generation agents can also be effective and well-tolerated by patients. The addition of a sedating first generation antihistamine to a second generation antihistamine may help patients sleep better.²⁻³ For the treatment of atopic dermatitis, topical corticosteroids are the standard of care.⁶⁻⁷ Antihistamines may help relieve pruritic symptoms, especially in those with concomitant urticaria or allergic rhinitis.⁷ First generation antihistamines may also be useful in patients with sleep disturbances due to pruritus.⁶⁻⁸ For the management of allergic/atopic conjunctivitis, topical antihistamines are an effective treatment option; however, oral antihistamines may also be considered.⁸ Antihistamines are not recommended for the treatment of acute sinusitis. They may have a role in the management of chronic sinusitis if allergic rhinitis is an underlying risk factor.^{10,13-14} The available guidelines do not give preference to one particular first generation antihistamine over another.^{1-3,5-15}

There are very few studies that directly compare the first generation antihistamines. Clemastine and chlorpheniramine were found to be equally effective for the treatment of allergic rhinitis.²³⁻²⁵ The first generation antihistamines have also been shown to be as effective as second generation antihistamines in multiple studies.^{19,21-29,31,36} The fixed-dose combination of triprolidine-pseudoephedrine was shown to be more effective than monotherapy with triprolidine or pseudoephedrine.³²⁻³⁴ However, there were no studies found in the medical literature that directly compared the efficacy of the fixed-dose combination product to the coadministration of each component as separate formulations. Several clinical trials have evaluated the central nervous system effects of antihistamines. The first generation antihistamines have been shown to adversely affect cognitive and psychomotor functions, as well as impair driving performance.³⁸⁻⁶¹

Oral decongestants (pseudoephedrine and phenylephrine) help to relieve nasal congestion and are available in combination with several of the first generation antihistamines. Pseudoephedrine has been used to make methamphetamine and there are restrictions on the sale of this product in the United States. Many over-the-counter products now contain phenylephrine; however, phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut.¹

There is insufficient evidence to support that one brand first generation antihistamine is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand first generation antihistamine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Wallace DV, Dykewicz MS, Bernstein DI, et al. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol*. 2008;122(2 Suppl):S1-84.
2. Grattan C, Humphreys F, British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol* 2007;157:1116-23.
3. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Diagnosis and Management of Urticaria: A Practice Parameter. *J Allergy Clin Immunol*. 2014;133:1270-1277.
4. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Jan 2017]. Available from: <http://online.factsandcomparisons.com>.
5. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis--a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015 Nov;115(5):341-84.
6. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines for the management of atopic dermatitis. *J Am Acad Dermatol*. 2014;71(1):116-132.
7. Sidbury R, Davis DM, Cohen DE, et al. Guidelines for the management of atopic dermatitis. *J Am Acad Dermatol*. 2014;71(2):327-349.
8. Schneider L, Tilles S, Lio P, et al. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Atopic dermatitis: A practice parameter update 2012. *J Allergy Clin Immunol*. 2013; 131:295-299.
9. American Academy of Ophthalmology (AAO) Cornea/External Disease Panel. Preferred Practice Patterns® Guidelines. Conjunctivitis-Limited Revision [guideline on the internet]. San Francisco (CA): AAO; 2013 [cited 2014 Sep]. Available from: <http://one.aao.org/preferred-practice-pattern/conjunctivitis-ppp--2013>.
10. Snellman L, Adams W, Anderson G, Godfrey A, Gravley A, Johnson K, Marshall P, Myers C, Nesse R, Short S. Institute for Clinical Systems Improvement. Diagnosis and Treatment of Respiratory Illness in Children and Adults. <http://bit.ly/RespIll>. Updated January 2013.
11. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010 Sep;126(3):466-76.
12. Price D, Bond C, Bouchard J, Costa R, Keenan J, Levy ML, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of allergic rhinitis. *Prim Care Respir J*. 2006 Feb;15(1):58-70.
13. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015 Apr;152(2 Suppl):S1-S39.
14. Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol*. 2014 Oct;113(4):347-85.
15. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, Church MK, Ensina LF, Gimenez-Arnau A, Godse K, Goncalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Abdul Latiff AH, Mathelier-Fusade P, Metz M, Nast A, Saini SS, Sanchez-Borges M, Schmid-Grendelmeier P, Simons FER, Staubach P, Sussman G, Toubi E, Vena GA, Wedi B, Zhu XJ, Maurer M. The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014; DOI: 10.1111/all.12313.
16. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Jan]. Available from: <http://www.thomsonhc.com/>.
17. Daily Med [database on the internet]. Bethesda (MD): National Library of Medicine; 2017 [cited 2017 Jan]. Available at: <http://dailymed.nlm.nih.gov/dailymed/about.cfm>.
18. Druce HM, Thoden WR, Mure P, et al. Brompheniramine, loratadine, and placebo in allergic rhinitis: a placebo-controlled comparative clinical trial. *J Clin Pharmacol*. 1998;38:382-9.
19. Crawford WW, Klaustermeyer WB, Lee PH, et al. Comparative efficacy of terfenadine, loratadine, and astemizole in perennial allergic rhinitis. *Otolaryngol Head Neck Surg*. 1998;118:668-73.
20. von Maur K. Antihistamine selection in patients with allergic rhinitis. *Ann Allergy*. 1985;55:458-62.
21. Prevost M, Turenne Y, Moote DW, et al. Comparative study of SCH 434 and CTM-D in the treatment of seasonal allergic rhinitis. *Clin Ther*. 1994;16:50-6.
22. Gibbs TG, Irander K, Salo OP. Acrivastine in seasonal allergic rhinitis: two randomized crossover studies to evaluate efficacy and safety. *J Int Med Res*. 1988;16:413-9.

23. Sheriff JM, Wallace MG. A comparative study of clemastine ('Tavegil') and chlorpheniramine maleate in the treatment of hay fever. *Curr Med Res Opin.* 1976;4:245-9.
24. Thomas JS, Heurich AE, Ralph JW, et al. Double-blind, controlled study of clemastine fumarate, chlorpheniramine and placebo in patients with seasonal allergic rhinitis. *Ann Allergy* 1977;38:169-74.
25. Todd G, Hopkins P, Maclay WP. Double-blind trials of clemastine ('Tavegil') in allergic rhinitis. *Curr Med Res Opin.* 1975;3:126-31.
26. Dockhorn RJ, Bergner A, Connell JT, et al. Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. *Ann Allergy.* 1987;58:407-11.
27. Frølund L, Etholm B, Irander K, et al. A multicentre study of loratadine, clemastine and placebo in patients with perennial allergic rhinitis. *Allergy.* 1990;45:254-61.
28. Irander K, Odkvist LM, Ohlander B. Treatment of hay fever with loratadine--a new non-sedating antihistamine. *Allergy.* 1990;45:86-91.
29. Boner AL, Miglioranza P, Richelli C, et al. Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis. *Allergy.* 1989;44:437-41.
30. Raphael GD, Angello JT, Wu MM, et al. Efficacy of diphenhydramine vs desloratadine and placebo in patients with moderate-to-severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 2006;96:606-14.
31. Park JH, Godbold JH, Chung D, Sampson HA, Wang J. Comparison of cetirizine and diphenhydramine in the treatment of acute food-induced allergic reactions. *J Allergy Clin Immunol.* 2011 Nov;128(5):1127-8.
32. Connell JT, Williams BO, Allen S, et al. A double-blind controlled evaluation of Actifed and its individual constituents in allergic rhinitis. *J Int Med Res.* 1982;10:341-7.
33. Diamond L, Gerson K, Cato A, et al. An evaluation of triprolidine and pseudoephedrine in the treatment of allergic rhinitis. *Ann Allergy.* 1981;47:87-91.
34. Empey DW, Bye C, Hodder M, et al. A Double-blind crossover trial of pseudoephedrine and triprolidine, alone and in combination, for the treatment of allergic rhinitis. *Ann Allergy.* 1975;34:41-6.
35. Jolliffe DS, Sim-Davis D, Templeton JS. A placebo-controlled comparative study of sustained-release brompheniramine maleate against clemastine fumarate in the treatment of chronic urticaria. *Curr Med Res Opin.* 1985;9:394-9.
36. Gale AE, Harvey SG, Calthrop JG, et al. A comparison of acrivastine versus chlorpheniramine in the treatment of chronic idiopathic urticaria. *J Int Med Res.* 1989;17 (Suppl 2):25B-27B.
37. Bye CE, Cooper J, Empey DW, et al. Effects of pseudoephedrine and triprolidine, alone and in combination, on symptoms of the common cold. *Br Med J.* 1980;281:189-90.
38. Seppälä T, Nuotto E, Korttila K, et al. Single and repeated dose comparison of three antihistamines and phenylpropanolamine: psychomotor performance and subjective appraisals of sleep. *Br J Clin Pharmacol.* 1981;12:179-88.
39. Nicholson AN. Effect of the antihistamines, brompheniramine maleate and triprolidine hydrochloride, on performance in man. *Br J Clin Pharmacol.* 1979;8:321-4.
40. Ng KH, Chong D, Wong CK, et al. Central nervous system side effects of first- and second-generation antihistamines in school children with perennial allergic rhinitis: a randomized, double-blind, placebo-controlled comparative study. *Pediatrics.* 2004;113:e116-21.
41. Kamei H, Noda Y, Ishikawa K, et al. Comparative study of acute effects of single doses of fexofenadine, olopatadine, d-chlorpheniramine and placebo on psychomotor function in healthy volunteers. *Hum Psychopharmacol.* 2003;18:611-8.
42. Hindmarch I. The effects of the sub-chronic administration of an anti-histamine, clemastine, on tests of car driving ability and psychomotor performance. *Curr Med Res Opin.* 1976;4:197-206.
43. Cohen AF, Hamilton MJ, Peck AW, et al. The effects of acrivastine (BW825C), diphenhydramine and terfenadine in combination with alcohol on human CNS performance. *Eur J Clin Pharmacol.* 1987;32:279-88.
44. Ramaekers JG, O'Hanlon JF. Acrivastine, terfenadine and diphenhydramine effects on driving performance as a function of dose and time after dosing. *Eur J Clin Pharmacol.* 1994;47:261-6.
45. Vuurman EF, van Veggel LM, Sanders RL, et al. Effects of semprex-D and diphenhydramine on learning in young adults with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 1996;76:247-52.
46. Simons FE, Fraser TG, Reggin JD, et al. Comparison of the central nervous system effects produced by six H1-receptor antagonists. *Clin Exp Allergy.* 1996;26:1092-7.
47. Schweitzer PK, Muehlbach MJ, Walsh JK, et al. Sleepiness and performance during three-day administration of cetirizine or diphenhydramine. *J Allergy Clin Immunol.* 1994;94:716-24.
48. Simons FE, Fraser TG, Maher J, et al. Central nervous system effects of H1-receptor antagonists in the elderly. *Ann Allergy Asthma Immunol.* 1999;82:157-60.

49. Vuurman EF, Rikken GH, Muntjewerff ND, et al. Effects of desloratadine, diphenhydramine, and placebo on driving performance and psychomotor performance measurements. *Eur J Clin Pharmacol.* 2004;60:307-13.
50. Wilken JA, Kane RL, Ellis AK, et al. A comparison of the effect of diphenhydramine and desloratadine on vigilance and cognitive function during treatment of ragweed-induced allergic rhinitis. *Ann Allergy Asthma Immunol.* 2003;91:375-85.
51. Mansfield L, Mendoza C, Flores J, et al. Effects of fexofenadine, diphenhydramine, and placebo on performance of the test of variables of attention (TOVA). *Ann Allergy Asthma Immunol.* 2003;90:554-9.
52. Weiler JM, Bloomfield JR, Woodworth GG, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. *Ann Intern Med.* 2000;132:354-63.
53. Gandon JM, Allain H. Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers. *Br J Clin Pharmacol.* 2002;54:51-8.
54. Verster JC, Volkerts ER, van Oosterwijk AW, et al. Acute and subchronic effects of levocetirizine and diphenhydramine on memory functioning, psychomotor performance, and mood. *J Allergy Clin Immunol.* 2003;111:623-7.
55. Verster JC, de Weert AM, Bijtjes SI, et al. Driving ability after acute and sub-chronic administration of levocetirizine and diphenhydramine: a randomized, double-blind, placebo-controlled trial. *Psychopharmacology (Berl).* 2003;169:84-90.
56. Bender BG, McCormick DR, Milgrom H, et al. Children's school performance is not impaired by short-term administration of diphenhydramine or loratadine. *J Pediatr.* 2001;138:656-60.
57. Kay GG, Berman B, Mockoviak SH, et al. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. *Arch Intern Med.* 1997;157:2350-6.
58. Vuurman EF, van Veggel LM, Uiterwijk MM, et al. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy.* 1993;71:121-6.
59. Roth T, Roehrs T, Koshorek G, et al. Sedative effects of antihistamines. *J Allergy Clin Immunol* 1987;80:94-8.
60. Witek TJ Jr, Canestrari DA, Miller RD, et al. Characterization of daytime sleepiness and psychomotor performance following H1 receptor antagonists. *Ann Allergy Asthma Immunol.* 1995;74:419-26.
61. Cohen AF, Hamilton M, Philipson R, et al. The acute effects of acrivastine (BW825C), a new antihistamine, compared with triprolidine on measures of central nervous system performance and subjective effects. *Clin Pharmacol Ther.* 1985;38:381-6.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Estrogens
AHFS Class 681604
May 10, 2017**

I. Overview

The estrogens are approved for the treatment of vasomotor symptoms associated with menopause, vulvar and vaginal atrophy, abnormal uterine bleeding, hypoestrogenism, prevention of postmenopausal osteoporosis, as well as for the palliative treatment of prostate and breast cancer.¹⁻³² The menopausal transition period is associated with irregular or heavy bleeding, hot flashes, sleep disturbance, vaginal dryness, sexual dysfunction, incontinence, urinary tract infections, depression, and other clinical manifestations. For most women, these symptoms are usually mild and of short duration. The use of hormone therapy helps to alleviate these symptoms. Estrogen can be used alone in women who have had a hysterectomy; however, a progestin should be added to the regimen for women with an intact uterus as it reduces the risk of endometrial cancer.³³⁻⁴⁵

For over 20 years, studies have examined the role of hormone therapy in the prevention of chronic diseases.⁴⁴ Observational studies suggested that there was a lower risk of cardiovascular disease, colorectal cancer, and osteoporotic fractures with the use of hormone therapy.⁴⁶ The Women’s Health Initiative (WHI) studies were designed to further assess the effects of hormone therapy on these end points. Women with an intact uterus were enrolled in the estrogen-plus-progestin therapy (EPT) trial, whereas women without a uterus were enrolled in the estrogen-alone therapy (ET) study. The EPT substudy was stopped early due to an increased risk for cardiovascular events, stroke, pulmonary emboli, venous thromboembolic events, and invasive breast cancer.⁴⁷ The ET substudy was also stopped early due to an increased risk of stroke and no benefit with regards to cardiovascular disease.⁴⁸ Two additional long-term trials (HERS and HERS II) also failed to show a benefit with hormone therapy for the primary or secondary prevention of cardiovascular disease.⁴⁹ The Food and Drug Administration requested that the manufacturers of estrogen products revise their product labeling to include updated safety information from the WHI studies.⁵⁰⁻⁵¹ Many organizations recommend the use of hormone therapy only for the short-term treatment of menopausal symptoms. The long-term use of hormone therapy is no longer recommended for the prevention of chronic diseases.^{35,41-44}

The estrogens are available in a variety of dosage forms, including injectable, oral, topical, transdermal, and vaginal preparations. Oral estrogens have a greater effect on the liver than topical formulations due to first-pass metabolism following gastrointestinal absorption. Oral estrogens may increase the production of cholesterol (triglycerides and high density lipoprotein cholesterol) and clotting factors, which is only minimally affected by topical, transdermal, and vaginal preparations.⁵²

Conjugated estrogens-bazedoxifene bind to and activate estrogen receptors alpha and beta, which vary in proportion from tissue to tissue. Bazedoxifene is a third generation selective estrogen receptor modulator which acts as an agonist in some tissues and as an antagonist in the uterus. The pairing of conjugated estrogens with bazedoxifene produces a composite effect specific to each tissue. The addition of bazedoxifene reduces the risk of endometrial hyperplasia associated with the conjugated estrogens component.^{1,32}

The estrogens that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Estradiol, estradiol valerate, estradiol-norethindrone, estropipate, and norethindrone-ethinyl estradiol are available in a generic formulation. This class was last reviewed in February 2015.

Table 1. Estrogens Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Estradiol	tablet, topical gel, topical spray, transdermal patch, vaginal cream, vaginal ring, vaginal tablet	Alora ^{®*} , Climara ^{®*} , Divigel [®] , Elestrin [®] , Estrace ^{®*} , Estring [®] , Evamist [®] , Menostar [®] , Minivelle ^{®*} , Vagifem ^{®*} , Vivelle-Dot ^{®*}	estradiol

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Estradiol acetate	vaginal ring	Femring®	none
Estradiol cypionate	injection	Depo-Estradiol®	none
Estradiol valerate	injection	Delestrogen®*	estradiol valerate
Estradiol and drospirenone	tablet	Angeliq®	none
Estradiol and levonorgestrel	transdermal patch	Climara Pro®	none
Estradiol and norethindrone	tablet, transdermal patch	Activella®*, Amabelz®*, Combipatch®, Mimvey®*	estradiol and norethindrone
Estradiol and norgestimate	tablet	Prefest®	none
Estrogens, conjugated	injection, tablet, vaginal cream	Premarin®	Premarin® (tablets only)
Estrogens, conjugated, synthetic B	tablet	Enjuvia®	none
Estrogens, conjugated and bazedoxifene	tablet	Duavee®	none
Estrogens, conjugated and medroxyprogesterone	tablet	Premphase®, Prempro®	none
Estrogens, esterified	tablet	Menest®	Menest®
Estropipate	tablet	N/A	estropipate
Norethindrone and ethinyl estradiol	tablet	FemHRT®*, Jevantique®*, Jinteli®*	norethindrone and ethinyl estradiol

*Generic is available in at least one dosage form or strength.
N/A=not applicable, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the estrogens are summarized in Table 2.

Table 2. Treatment Guidelines Using the Estrogens

Clinical Guideline	Recommendation(s)
<p>The International Menopause Society, The North American Menopause Society, The Endocrine Society, The European Menopause and Andropause Society, The Asia Pacific Menopause Federation, The International Osteoporosis Foundation, and The Federation of Latin American Menopause Societies: Revised Global Consensus Statement on Menopausal Hormone Therapy (2016)³³</p>	<p>Benefit/risk profile of menopausal hormone therapy (MHT)</p> <ul style="list-style-type: none"> MHT (including tibolone and the combination of conjugated equine estrogens and bazedoxifene) is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause. If MHT is contraindicated or not desired for treatment of vasomotor symptoms, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors such as paroxetine, escitalopram, venlafaxine and desvenlafaxine, which have been shown to be effective in randomized controlled trials (RCTs), may be considered. Gabapentin may also be considered. Quality of life, sexual function and other menopause-related complaints, such as joint and muscle pains, mood changes and sleep disturbances, may improve during MHT. MHT is effective in the prevention of bone loss and has been shown to significantly lower the risk of hip, vertebral and other osteoporosis-related fractures in postmenopausal women. MHT is the only therapy available with RCT-proven efficacy of fracture reduction in a group of postmenopausal women not selected for being at risk of fracture and with mean T-scores in the normal to osteopenic range. MHT, including tibolone, can be initiated in postmenopausal women at risk of fracture or osteoporosis before the age of 60 years or within 10 years after menopause. Initiation of MHT after the age of 60 years for the indication of fracture

Clinical Guideline	Recommendation(s)
	<p>prevention is considered second-line therapy and requires individually calculated benefit/risk, compared to other approved drugs. If MHT is elected, the lowest effective dose should be used.</p> <ul style="list-style-type: none"> • MHT, including tibolone, is effective in the treatment of vulvovaginal atrophy (VVA), now also considered as a component of the genitourinary syndrome of menopause (GSM). Local low-dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse or for the prevention of recurrent urinary tract infections. Ospemifene, an oral selective estrogen receptor modulator, is also licensed in some countries for the treatment of dyspareunia attributed to VVA. • RCTs and observational data as well as meta-analyses provide evidence that standard-dose estrogen-alone MHT may decrease the risk of myocardial infarction and all-cause mortality when initiated in women younger than 60 years of age and/or within 10 years of menopause. Data on estrogen plus progestogen MHT initiated in women younger than age 60 years or within 10 years of menopause show a less compelling trend for mortality benefit, and evidence on cardioprotection is less robust with inconsistent results compared to the estrogen-alone group. • The risk of venous thromboembolism (VTE) and ischemic stroke increases with oral MHT, although the absolute risk of stroke with initiation of MHT before age 60 years is rare. Observational studies and a meta-analysis point to a probable lower risk of VTE and possibly stroke with transdermal therapy (0.05 mg twice weekly or lower) compared to oral therapy. • The risk of breast cancer in women over 50 years of age associated with MHT is a complex issue with decreased risk reported from RCTs for estrogen alone (conjugated equine estrogens in the Women's Health Initiative (WHI)) in women with hysterectomy and a possible increased risk when combined with a progestin (medroxyprogesterone acetate in the WHI) in women without hysterectomy. The increased risk of breast cancer thus seems to be primarily, but not exclusively, associated with the use of a progestin with estrogen therapy in women without hysterectomy and may be related to the duration of use. • The risk of breast cancer attributable to MHT is rare. It equates to an incidence of <1.0 per 1000 women per year of use. This is similar or lower than the increased risk associated with common factors such as sedentary lifestyle, obesity and alcohol consumption. The risk may decrease after treatment is stopped, but data are inconsistent. • Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years are at a higher risk for cardiovascular disease and osteoporosis and may be at increased risk of affective disorders and dementia. In such women, MHT reduces symptoms and preserves bone density. Observational studies that suggest MHT is associated with reduced risk of heart disease, longer lifespan, and reduced risk of dementia require confirmation in RCTs. MHT is advised at least until the average age of menopause. • MHT initiated in early menopause has no substantial effect on cognition, but, based on observational studies, it may prevent Alzheimer's disease in later life. In RCTs, oral MHT initiated in women aged 65 years or older also has no substantial effect on cognition and increases the risk of dementia. • MHT may be beneficial in improving mood in early postmenopausal women with depressive and/or anxiety symptoms. MHT may also be beneficial for perimenopausal women with major depression but antidepressant therapy remains first-line treatment in this setting. <p>General principles governing the use of MHT</p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • The option of MHT is an individual decision in terms of quality of life and health priorities as well as personal risk factors such as age, time since menopause, and the risk of venous thromboembolism, stroke, ischemic heart disease, and breast cancer. MHT should not be recommended without a clear indication for its use. • Consideration of MHT for symptom relief or osteoporosis prevention should be a part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health and quality of life of peri- and postmenopausal women. • MHT includes a wide range of hormonal products and routes of administration, including tibolone (where available) or conjugated equine estrogens/bazedoxifene, with potentially different risks and benefits. However, evidence regarding differences in risks and benefits between different products is limited. • The type and route of administration of MHT should be consistent with treatment goals, patient preference and safety issues and should be individualized. The dosage should be titrated to the lowest appropriate and most effective dose. • Duration of treatment should be consistent with the treatment goals of the individual, and the benefit/risk profile needs to be individually reassessed annually. This is important in view of new data indicating longer duration of vasomotor symptoms in some women. • Estrogen as a single systemic agent is appropriate in women after hysterectomy but concomitant progestogen is required in the presence of a uterus for endometrial protection with the exception that conjugated equine estrogens can be combined with bazedoxifene for uterine protection. • The use of continuous testosterone therapy, either alone or with MHT, is supported in carefully selected postmenopausal women with sexual interest/arousal disorder (in countries with regulatory approval). • The use of custom-compounded hormone therapy is not recommended because of lack of regulation, rigorous safety and efficacy testing, batch standardization, and purity measures. • Current safety data do not support the use of MHT in breast cancer survivors.
<p>North American Menopause Society: Management of Osteoporosis in Postmenopausal Women: 2010 Position Statement (2010)³⁴</p>	<ul style="list-style-type: none"> • The primary indication for estrogen therapy (ET) and combined estrogen-progestogen therapy (EPT) is to treat moderate-to-severe menopausal symptoms. • The primary goal of osteoporosis therapy is fracture prevention. This is accomplished by slowing or stopping bone loss, maintaining bone strength, and minimizing or eliminating factors that may contribute to fractures. • ET/EPT should be used at the lowest effective dose consistent with treatment goals. Lower doses of ET/EPT than used in the Women's Health Initiative have not been examined with regard to fracture efficacy. • Extended use of hormone therapy is an option for women who have established reduction in bone mass, regardless of menopause symptoms, for prevention of further bone loss and/or reduction of osteoporotic fracture when other therapies are not appropriate or cause side effects, or when the benefits of extended use are expected to exceed the risks.
<p>North American Menopause Society: The 2012 Hormone Therapy Position Statement (2012)³⁵</p>	<p><u>Benefits and risks of hormone therapy</u></p> <ul style="list-style-type: none"> • Estrogen therapy (ET) with or without a progestogen is the most effective treatment of menopause-related vasomotor symptoms and their potential consequences, such as diminished sleep quality, irritability, difficulty concentrating, and subsequently reduced quality of life. Treatment of moderate to severe vasomotor symptoms remains the primary indication for

Clinical Guideline	Recommendation(s)
	<p>hormone therapy (HT).</p> <ul style="list-style-type: none"> • ET is the most effective treatment of moderate to severe symptoms of vulvar and vaginal atrophy (e.g., vaginal dryness, dyspareunia, and atrophic vaginitis). Some low dose systemic regimens may be inadequate for the relief of vaginal symptoms and may require the addition of low-dose local ET to achieve the desired results. When ET is considered solely for treatment of vaginal atrophy, local vaginal ET is advised. • A significant effect of ET on sexual interest, arousal, and orgasmic response independent from its role in treating menopausal symptoms is not supported by current evidence. • When alternate osteoporosis therapies are not appropriate or cause adverse effects, the extended use of HT is an option for women who are at high risk of osteoporotic fracture. There is no evidence that HT stops working with long-term treatment; however, the benefits of HT on bone mass and fracture reduction dissipate quickly after the discontinuation of treatment, necessitating a transition to a different osteoporosis treatment (or prevention strategy) to preserve bone mass. • HT is currently not recommended for coronary protection in women of any age. Initiation of HT by women ages 50 to 59 years or by those within 10 years of menopause to treat typical menopausal symptoms does not seem to increase the risk of coronary heart disease (CHD) events. There is emerging evidence that the initiation of ET in early postmenopause may reduce coronary artery disease and CHD risk. • Unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk related to the ET dose and duration of use. To negate this increased risk, adequate concomitant progestogen is recommended for women with an intact uterus when using systemic ET. In general, HT is not recommended in women with a history of endometrial cancer. • Diagnosis of breast cancer increases with estrogen-progestogen therapy (EPT) use beyond three to five years. For all outcomes, the absolute risk of events in younger women is lower than that for older women. HT use in breast cancer survivors may be associated with an increased risk of recurrence. Published data on the role of HT and risk of ovarian cancer are conflicting. ET was associated with a higher risk of ovarian cancer than EPT. The association between ovarian cancer and EPT use beyond five years would fall into the rare- or very rare-risk category. Women at increased risk of ovarian cancer (e.g., those with a family history or a BRCA mutation) should be counseled about this potential association. • HT may reduce total mortality when initiated soon after menopause. The Women's Health Initiative suggests that both ET and EPT nonsignificantly reduce total mortality by 30% when initiated in women younger than 60 years and that when data from the ET and EPT arms were combined, that reduction was statistically significant. <p><u>Practical therapeutic issues</u></p> <ul style="list-style-type: none"> • The primary menopause-related indication for progestogen use is to negate the increased risk of endometrial cancer from systemic ET use. All women with an intact uterus who use systemic ET should also be prescribed adequate progestogen. With occasional exceptions (e.g., history of extensive endometriosis), postmenopausal women without a uterus should not be prescribed a progestogen with systemic ET. • The lowest effective dose of estrogen consistent with treatment goals, benefits, and risks for the individual woman should be the therapeutic goal, with an appropriate dose of progestogen added to counter the adverse effects of systemic ET on the uterus.

Clinical Guideline	Recommendation(s)
	<p><u>Duration of use</u></p> <ul style="list-style-type: none"> • Recommendations for duration of use differ between ET and EPT. Given the more favorable safety profile of ET, it could be considered for longer duration of therapy in the absence of adverse effects and risk factors. Women experiencing premature menopause are at increased risk of osteoporosis and, possibly, cardiovascular disease, and they often experience more intense symptoms than do women reaching menopause at the median age. Therefore, HT generally is advised for these young women until the median age of menopause when treatment should be reassessed. • For EPT, duration is limited by the increased risk of breast cancer and breast cancer mortality associated with three to five years of use; for ET, a more favorable benefit risk profile was observed during a mean of seven years of use and four years of follow-up, a finding that allows more flexibility in duration of use. • Individualization is of key importance in the decision to use HT and should incorporate the woman's health and quality of life priorities as well as her personal risk factors, such as risk of venous thrombosis, CHD, stroke, and breast cancer.
<p>The North American Menopause Society: Statement on Continuing Use of Systemic Hormone Therapy After Age 65 (2015)³⁶</p>	<ul style="list-style-type: none"> • Provided that the woman has been advised of the increase in risks associated with continuing hormone therapy beyond age 60 years and has clinical supervision, extending hormone therapy use with the lowest effective dose is acceptable under some circumstances, such as for the woman who has persistent bothersome menopausal symptoms and for whom her clinician has determined that the benefits of menopause symptom relief outweigh the risks. • Use of hormone therapy should be individualized and not discontinued solely based on a woman's age. • The decision to continue or discontinue hormone therapy should be made jointly by the woman and her healthcare provider.
<p>European Menopause and Andropause Society: Maintaining postreproductive health: A care pathway (2016)³⁷</p>	<p><u>Menopausal hormone therapy (MHT) general considerations</u></p> <ul style="list-style-type: none"> • Administration of systemic MHT has a favorable risk–benefit profile for women under the age of 60 years or within 10 years after menopause for menopausal symptoms and osteoporosis. • MHT at very low doses or non-estrogen-based therapies should be considered for older women. • Symptoms due to the genitourinary syndrome of the menopause can be managed with low-dose topical estrogens or non-hormonal therapies. • Prevention and management of cardiovascular disease should be undertaken in accordance with international and national guidelines. • MHT should not be used primarily for the primary or secondary prevention of cognitive decline or dementia. • Estrogen alone is given to hysterectomized women. Progestogens and the selective estrogen receptor modulator bazedoxifene are added in regimens for non-hysterectomized women to reduce the increased risk of endometrial hyperplasia and carcinoma which occurs with unopposed estrogen. Tibolone is a synthetic steroid compound that is in itself inert, but whose metabolites have estrogenic, progestogenic and androgenic actions. It is classified as MHT. <p><u>The main benefits of MHT</u></p> <ul style="list-style-type: none"> • MHT is the most effective treatment for vasomotor symptoms. • Systemically administered MHT and topical estrogens are effective in the management of symptoms of vulvar and vaginal atrophy. • MHT prevents postmenopausal bone loss.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • MHT may aid in the management of low mood that results from menopause. • Standard-dose estrogen-alone MHT may decrease coronary heart disease and all-cause mortality in women younger than 60 years of age and within 10 years of menopause. <p><u>The main risks of MHT</u></p> <ul style="list-style-type: none"> • Estrogen-alone MHT increases the risk of endometrial cancer. • Oral, but not transdermal, estrogens increase the risk of venous thromboembolism. • Combined MHT, but not estrogen-alone MHT, may be associated with an increased risk of breast cancer; this risk seems to be lost when MHT is discontinued. • MHT may confer a small increased risk of stroke: there is a suggestion that transdermal preparations have less impact on the risk of stroke than oral preparations • MHT use over the age of 65 years may cause deterioration in cognitive function. • Initiation of standard-dose oral MHT in women over the age of 60 years who have established atherosclerosis may not result in a decreased risk of coronary heart events.
<p>National Osteoporosis Foundation: Clinician's Guide to Prevention and Treatment of Osteoporosis (2014)³⁸</p>	<p><u>Universal recommendations for all patients</u></p> <ul style="list-style-type: none"> • Adequate intake of calcium and vitamin D: If adequate dietary calcium cannot be obtained, dietary supplementation is indicated up to the recommended daily intake. <ul style="list-style-type: none"> ○ Recommendations are for men age 50 to 70 to consume 1,000 mg per day of calcium and that women age ≥ 51 and men age ≥ 71 to consume 1,200 mg per day of calcium. There is no evidence that calcium intake in excess of these amounts confers additional bone strength. ○ Vitamin D recommended daily intake for adults age 50 and older is 800 to 1,000 international units. • Regular weight-bearing and muscle-strengthening exercises reduce the risk of falls and fractures. • Tobacco smoking and excessive alcohol intake should be avoided. <p><u>Pharmacologic therapy</u></p> <ul style="list-style-type: none"> • Postmenopausal women and men age 50 and older presenting with the following should be considered for treatment: <ul style="list-style-type: none"> ○ A hip or vertebral fracture. ○ T-score ≤ -2.5 at the femoral neck, total hip, or lumbar spine. ○ Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or lumbar spine and a 10 year probability of a hip fracture $\geq 3\%$ or a 10 year probability of a major osteoporosis-related fracture $\geq 20\%$). • Current FDA-approved pharmacologic options for osteoporosis are bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid), calcitonin, estrogen agonist/antagonist (raloxifene), estrogens and/or hormone therapy, tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone (teriparatide), and RANK ligand inhibitor (denosumab). • No pharmacologic therapy should be considered indefinite in duration. After the initial treatment period, which depends on the pharmacologic agent, a comprehensive risk assessment should be performed. There is no uniform recommendation that applies to all patients and duration decisions need to be individualized. • Sequential treatment with anabolic therapy followed by an antiresorptive agent is generally preferred. Combination therapy with teriparatide and an

Clinical Guideline	Recommendation(s)
	<p>antiresorptive can be considered in a few clinical settings in patients with very severe osteoporosis such as spine and hip fractures. There are few indications for combining two antiresorptive treatments, but such options could be considered in the short-term in women who are experiencing active bone loss while on low dose HT for menopausal symptoms or raloxifene for breast cancer prevention.</p>
<p>North American Menopause Society: Management of symptomatic vulvovaginal atrophy: 2013 position statement (2013)³⁹</p>	<ul style="list-style-type: none"> • First-line therapies for women with symptomatic vulvovaginal atrophy (VVA) include nonhormonal lubricants with intercourse and, if indicated, regular use of long-acting vaginal moisturizers. • For symptomatic women with moderate to severe VVA and for those with milder VVA who do not respond to lubricants and moisturizers, estrogen therapy either vaginally at low-dose or systemically remains the therapeutic standard. Low-dose vaginal estrogen is preferred when VVA is the only menopausal symptom. • Ospemifene is another option for dyspareunia. • For women with a history of breast or endometrial cancer, management depends on a woman's preference, need, understanding of potential risks, and consultation with her oncologist. • Estrogen therapy carries a class effect of venous thromboembolism. Low-dose vaginal estrogen may carry a very low risk, but there has been no report of an increased risk in the vaginal estrogen clinical trials. Data in high-risk women are lacking. • A progestin is generally not indicated when low-dose vaginal estrogen is administered for symptomatic VVA. Endometrial safety data are not available for use longer than one year. • If a woman is at high risk of endometrial cancer or is using a higher dose of vaginal ET, transvaginal ultrasound or intermittent progestogen therapy may be considered. There are insufficient data to recommend routine annual endometrial surveillance in asymptomatic women using vaginal ET. • Spotting or bleeding in a postmenopausal woman who has an intact uterus requires a thorough evaluation that may include transvaginal ultrasound and/or endometrial biopsy. • For women treated for non-hormone-dependent cancer, management of VVA is similar to that for women without a cancer history. • Vaginal ET or ospemifene, with appropriate clinical surveillance, can be continued as long as bothersome symptoms are present. • Proactive education on vaginal health is recommended for postmenopausal women.
<p>American Heart Association: Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women: 2011 Update (2011)⁴⁰</p>	<ul style="list-style-type: none"> • Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used for the primary or secondary prevention of cardiovascular disease (CVD). • Other approaches such as lowering cholesterol and controlling blood pressure should be considered for cardiovascular disease prevention.
<p>International Menopause Society: Updated 2013 Recommendations on women's midlife health and menopause hormone therapy (2016)⁴¹</p>	<ul style="list-style-type: none"> • MHT remains the most effective therapy for vasomotor symptoms and urogenital atrophy. • Other menopause-related complaints, such as joint and muscle pains, mood swings, sleep disturbances and sexual dysfunction (including reduced libido) may improve during MHT. Quality of life and sexual function may also improve. • The administration of individualized MHT (including androgenic preparations when appropriate) may improve both sexuality and overall quality of life.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Consideration of MHT should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health of peri- and postmenopausal women. • MHT must be individualized and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, the woman’s preferences and expectations. • The risks and benefits of MHT differ for women during the menopause transition compared to those for older women. • MHT includes a wide range of hormonal products and routes of administration, with potentially different risks and benefits. Thus, the term ‘class effect’ is confusing and inappropriate. However, evidence regarding differences in risks and benefits between different products is limited. • Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years are at higher risk for cardiovascular disease and osteoporosis and may be at increased risk of affective disorders and dementia. MHT may reduce symptoms and preserve bone density and is advised at least until the average age of menopause. • Counselling should convey the benefits and risks of MHT in clear and comprehensible terms, e.g., as absolute numbers rather than, or in addition to, percentage changes from baseline expressed as a relative risk. This allows a woman and her physician to make a well-informed decision about MHT. Written information about risks and benefits as well as decision aids may be useful. • MHT should not be recommended without a clear indication for its use, i.e., significant symptoms or physical effects of estrogen deficiency. • Women taking MHT should have at least an annual consultation to include a physical examination, update of medical and family history, relevant laboratory and imaging investigations, a discussion on lifestyle, and strategies to prevent or reduce chronic disease. There is currently no indication for increased mammographic or cervical smear screening. • There are no reasons to place mandatory limitations on the duration of MHT. Data from the WHI trial and other studies support safe use for at least five years in healthy women initiating treatment before age 60 years. • Whether or not to continue therapy should be decided at the discretion of the well-informed woman and her health professional, dependent upon the specific goals and an objective estimation of ongoing individual benefits and risks. • The dosage should be titrated to the lowest effective dose. • Lower doses of MHT than previously used may reduce symptoms sufficiently and maintain quality of life for many women. However, long-term data on lower doses regarding fracture or cancer risks and cardiovascular implications are still lacking.
<p>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause (2011)⁴²</p>	<ul style="list-style-type: none"> • Menopausal hormone therapy may be appropriate for the relief of severe menopausal symptoms in selected postmenopausal women, on the basis of individually determined benefit-vs-risk profile. • Menopausal hormone therapy may be prescribed during the perimenopause and early menopause for relief of menopausal symptoms and treatment of vulvovaginal atrophy. • The use of the transdermal route of estrogen administration should be considered in order to avoid the hepatic “first-pass effect,” which may theoretically reduce the risk of thromboembolic disease. • The use of transvaginal estrogen may be considered to provide topical effects with less systemic absorption. • The dose of menopausal hormone therapy may be reduced with advancing

Clinical Guideline	Recommendation(s)
	<p>age.</p> <ul style="list-style-type: none"> • Because of the increased risk of endometrial cancer, unopposed estrogen should not be used in women with an intact uterus. • Progestational agents should be used for a minimum of 10 to 14 days per month in women treated with estrogen who have an intact uterus. • Long-cycle therapy with use of a progestogen for 14 days every three months may be considered, in an effort to reduce breast exposure to progestogens, despite lack of definitive assessment of efficacy. • Amenorrhea may be achieved by using a low dose of progestogen administered continuously (daily) in conjunction with estrogen. Because recent trials suggest adverse breast outcomes with continuous progesterone exposure, this form of therapy is not recommended. • Menopausal hormone therapy should be used in the lowest dose and for the shortest period necessary to control menopausal symptoms. • Therapeutic trials of nonhormonal prescription medications (e.g., clonidine, antidepressants, gabapentin) may also be considered for the relief of menopausal symptoms in women with no specific contraindications. • Over-the-counter supplements should be used with caution because they are not regulated by the United States FDA and have the potential for interactions with drugs and for causing harm. • Phytoestrogens, including soy-derived isoflavonoids, result in inconsistent relief of symptoms. Because these compounds may have estrogenic effects, women with a personal or strong family history of hormone-dependent cancers, thromboembolic events, or cardiovascular events should not use soy-based therapies. • Custom compounded “biochemical hormone therapy” is not recommended. • FDA-approved bioidentical hormone preparations may be considered, but evidence is lacking that they are safer or more effective compared to traditional forms of hormone therapy. • Menopausal hormone therapy should be used for the prevention and treatment of osteoporosis within the context of the overall benefit-vs-risk analysis of each patient. Data from multiple randomized-controlled trials substantiate the efficacy of estrogens in preserving bone mass, and less consistently, preventing fractures, but nonhormonal therapeutic options for bone health exist. • Hormone therapy for the prevention or treatment (or both) of dementia is not recommended. • Menopausal hormone therapy should be prescribed to women in conjunction with a thorough discussion of the possible relationship of menopausal hormone therapy to breast cancer. Current evidence suggests that estrogen/progestogen regimens are associated with a possible higher risk of breast cancer compared to estrogen therapy. • Concordant with current FDA warnings, it is recommended that women who are at increased risk of thromboembolic disease should not take estrogen-containing therapy. • Women should be advised that smoking increases the risk of cardiovascular and venous thromboembolic disease when taking estrogen, and aggressive smoking cessation programs should be advised. • Menopausal hormone therapy is not recommended for primary or secondary prevention of cardiovascular disease. • Lipid profiles, smoking history, and diabetes as well as family history should be assessed to assist in the determination of individual cardiovascular risk. • Women should be advised that cerebrovascular accidents occur with increased frequency in patients with estrogen alone or estrogen/progesterone therapy in an age-dependent manner.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Women should be advised that there may be an increase in ovarian epithelial tumors with the use of estrogen for more than ten years. • Women may be advised that several trials, including the WHI, have demonstrated a lower risk of colon cancer in women treated with estrogen/progesterone therapy. • The FDA has approved the use of menopausal hormone therapy for the following: <ul style="list-style-type: none"> ○ Treatment of moderate to severe vasomotor symptoms associated with menopause. Estrogen-containing products are the most effective approved therapies for these symptoms. ○ Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When estrogen is prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal preparations should be considered. • Prevention of postmenopausal osteoporosis. When menopausal hormone therapy is being prescribed solely for the prevention of postmenopausal osteoporosis, approved non-estrogen treatments should be carefully considered. Estrogen therapy and estrogen/progesterone therapy should be considered only in women with substantial risk of osteoporosis that outweighs the potential drug-related risks.
<p>Agency for Healthcare Research and Quality, United States Preventive Services Task Force: Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions (2012)⁴³</p>	<ul style="list-style-type: none"> • This recommendation applies to postmenopausal women who are considering hormone therapy for the primary prevention of chronic medical conditions. It does not apply to women who are considering hormone therapy to treat menopausal symptoms, such as hot flashes or vaginal dryness. • The chronic disease prevention benefits of combined estrogen and progestin do not outweigh the harms in most postmenopausal women. • The chronic disease prevention benefits of estrogen are unlikely to outweigh the harms in most postmenopausal women who have had a hysterectomy. • Although combined estrogen and progestin therapy (specifically, oral conjugated equine estrogen, 0.625 mg/day, plus medroxyprogesterone acetate, 2.5 mg/day) decreases the risk for fractures in postmenopausal women, there is an accompanying increased risk for serious adverse events, such as stroke, invasive breast cancer, dementia, gallbladder disease, deep venous thrombosis, and pulmonary embolism. • Estrogen therapy (specifically, oral conjugated equine estrogen, 0.625 mg/day) decreases the risk for fractures and has a small effect on the risk for invasive breast cancer, but it is also associated with important harms, such as an increased likelihood of stroke, deep venous thrombosis, and gallbladder disease. • Neither combined estrogen and progestin therapy nor estrogen alone reduces the risk for coronary heart disease in postmenopausal women.
<p>American College of Obstetricians and Gynecologists: Committee Opinion: Hormone Therapy and Heart Disease (2013)⁴⁴</p>	<ul style="list-style-type: none"> • Menopausal hormone therapy should not be used for the primary or secondary prevention of coronary heart disease at the present time. Evidence is insufficient to conclude that long-term estrogen therapy or hormone therapy use improves cardiovascular outcomes.
<p>Royal College of Obstetricians and Gynaecologists: Venous Thromboembolism and Hormone Replacement</p>	<ul style="list-style-type: none"> • The mechanism by which oral hormone replacement therapy provokes an increased risk of venous thromboembolism (VTE) is unclear. • Women initiating hormone replacement therapy should be counseled about the risk of VTE and the signs and symptoms of VTE. • Women should be advised to immediately seek medical help if they suspect that they have developed a thrombosis.

Clinical Guideline	Recommendation(s)
<p>Therapy (2011)⁴⁵</p>	<ul style="list-style-type: none"> • Women initiating or continuing hormone replacement therapy should be counseled on the perceived benefits and possible risks for their individual situations, including consideration of alternative therapies. • The risks of VTE in association with hormone replacement therapy may be influenced by the type of preparation and the duration of its use. • The risk of VTE may be less with esterified estrogens compared with conjugated equine estrogen. • There may be a greater risk of VTE with combination therapy and definitive information on individual estrogen types is still lacking. However, the results to date suggest that therapy with estrogen alone is associated with a significant VTE risk. • There is some evidence that the effect of estrogen therapy may be dose related. • Transdermal preparations are associated with a substantially lower risk of VTE compared to oral preparations. • The risk of VTE is highest in the first year of hormone replacement therapy, with no evidence of continuing risk on stopping hormone replacement therapy. • Universal screening of women for thrombophilic defects before prescribing or before continuing the prescription of hormone replacement therapy is inappropriate. • Oral hormone replacement therapy should be avoided in women without a personal history of VTE but with a high-risk thrombophilic trait that has been identified through screening because of a symptomatic family member. • A personal history of thrombosis is a contraindication to oral hormone replacement therapy. • If it is considered that quality of life is so severely affected that the benefits of hormone replacement therapy outweigh the risks, a transdermal preparation should be used. • It is recommended that hormone replacement therapy be discontinued when a women receiving therapy develops a VTE. • If it is considered desirable that a woman should continue hormone replacement therapy after a VTE has occurred on therapy, she should be referred to a clinician with special expertise in managing women at increased thrombotic risk requiring hormone replacement therapy. • Before initiating hormone replacement therapy, any personal or family history of VTE should be assessed. • A history of VTE in a first-degree relative is a relative contraindication to hormone replacement therapy. • When there is a family history of VTE in a first-degree relative, alternatives to oral hormone replacement therapy should be suggested. If hormone replacement therapy is considered desirable, transdermal preparations are associated with a significantly lower risk of venous thrombosis. • Hormone replacement therapy should be avoided in women with multiple pre-existing risk factors for VTE. • An individual assessment of the risks and benefits of stopping hormone replacement therapy before elective surgery is required for all women. Hormone replacement therapy may not need to be discontinued prior to surgery provided that appropriate thromboprophylaxis is utilized.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the estrogens are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Estrogens-Single Entity Products^{2-32,53}

Indications	Estradiol	Estradiol Acetate	Estradiol Cypionate	Estradiol Valerate	Estrogens, Conjugated Equine	Estrogens, Conjugated, Synthetic B	Estrogens, Esterified	Estropipate
Palliative treatment of advanced prostate cancer	✓ (Estrace ^{®*})			✓	✓ *		✓	
Palliative treatment of metastatic breast cancer	✓ (Estrace ^{®*})				✓ *		✓	
Prevention of postmenopausal osteoporosis	✓ (Alora [®] , Climara [®] , Estrace ^{®*} , Menostar [®] , Vivelle-Dot [®])				✓ *			✓
Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology					✓ †			
Treatment of atrophic vaginitis and kraurosis vulvae					✓ ‡			
Treatment of hypoenestrogenism due to hypogonadism, castration, or primary ovarian failure	✓ (Alora [®] , Climara [®] , Estrace ^{®*} , Vivelle-Dot [®])		✓	✓	✓ *		✓	✓
Treatment of vasomotor symptoms associated with menopause	✓ (Alora [®] , Climara [®] , Divigel [®] , Elestrin [®] , Estrace ^{®*} , Estrasorb [®] , Evamist [®] , Vivelle-Dot [®])	✓	✓	✓	✓ *	✓	✓	✓
Treatment of vulvar and vaginal atrophy associated with menopause	✓ (Alora [®] , Climara [®] , Estrace ^{®*} , Estring [®] , Vagifem [®] , Vivelle-Dot [®])	✓ §		✓	✓	✓	✓	✓
Treatment of vulvar and vaginal atrophy	✓ (Estrace ^{®‡})							

*Tablet formulation.

†Injection formulation.
‡Cream formulation.
§Vaginal ring formulation

Table 4. FDA-Approved Indications for the Estrogens-Combination Products^{2-32,53}

Indications	Estradiol and Drospirenone	Estradiol and Levonorgestrel	Estradiol and Norethindrone	Estradiol and Norgestimate	Estrogens, Conjugated and Bazedoxifene	Estrogens, Conjugated Equine and Medroxyprogesterone	Ethinyl Estradiol and Norethindrone
Prevention of postmenopausal osteoporosis		✓	✓ (Activella [®] , Amabelz [®] , Mimvey [®])	✓	✓	✓	✓
Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure			✓ (Combipatch [®])				
Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause	✓ (1/0.5 mg)		✓	✓		✓	
Treatment of moderate to severe vasomotor symptoms due to menopause	✓	✓	✓	✓	✓	✓	✓

IV. Pharmacokinetics

The pharmacokinetic parameters of the estrogens are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Estrogens¹

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
Single Entity Agents					
Estradiol	Transdermal: 20 times higher bioavailability compared to oral dosage forms	Primarily bound to SHBG and to albumin	Liver (primary) and skin (minimal). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary)	Transdermal (gel): Divigel [®] : 10 hours EstroGel [®] : 36 hours Transdermal (patch):

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
	Vaginal ring: 8%.			secretion of conjugates into the intestine)	Alora [®] : 1.75 hours Vivelle [®] : 4.4 hours Vivelle-Dot [®] : 5.9 to 7.7 hours
Estradiol acetate	Vaginal: rapidly absorbed for the first hour, followed by a decline to constant rate for the remaining three months	Primarily bound to SHBG and to albumin	Liver (primary). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Not reported
Estradiol cypionate	Intramuscular: absorbed over several weeks	Primarily bound to SHBG and to albumin	Liver (primary). Estrone and estriol are both active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine, hydrolyzed, and reabsorbed)	Not reported
Estradiol valerate	Intramuscular: absorbed over several weeks	Primarily bound to SHBG and to albumin	Liver (primary). Estrone and estriol are both active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine, hydrolyzed, and reabsorbed)	Not reported
Estrogens, conjugated Equine	Oral: well absorbed	Bound to albumin, SHBG, cortisol binding globulin, and α -1-glycoproteins	Liver (primary). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Oral (estrone): 26.5 to 26.7 hours
Estrogens, conjugated, synthetic B	Well absorbed	Primarily bound to SHBG and to albumin	Liver (primary). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide	14.26 hours (baseline-corrected estrone)

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
				and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	
Estrogens, esterified	Not reported	Primarily bound to SHBG and to albumin	Liver (primary). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Not reported
Estropipate	Well absorbed	Primarily bound to SHBG and to albumin	Liver (primary). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Not reported
Combination Products					
Estradiol and drospirenone	Drospirenone: 76 to 85% Estradiol: 53%	Drospirenone: 97% bound to serum proteins Estradiol: primarily bound to SHBG and to albumin	Drospirenone: liver (extensive) and cytochrome P450 3A4 isoenzyme (minor). No active metabolites Estradiol: liver (primary) and skin (minimal). Estradiol, estrone, and estriol are all active metabolite	Drospirenone: urine (38 to 47% as glucuronide and sulfate conjugates) and feces (17 to 20% as glucuronide and sulfate conjugates) Estradiol: urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Drospirenone: 36 to 42 hours Estradiol: not reported
Estradiol and levonorgestrel	Estradiol (transdermal): 20 times higher bioavailability compared to oral dosage forms	Estradiol: primarily bound to SHBG and to albumin Levonorgestrel: bound to	Estradiol: liver (primary) and skin (minimal). Estradiol, estrone, and estriol are all active metabolites	Estradiol: urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile	Estradiol: 1.75 to 77 hours Levonorgestrel: Not reported

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
	Levonorgestrel: not reported	SHBG and to albumin (97.5 to 99%)	Levonorgestrel: blood (extent unspecified). Activity of three metabolites not specified	(biliary secretion of conjugates into the intestine) Levonorgestrel: urine (45% of levonorgestrel and metabolites are excreted in the urine, mostly as glucuronide conjugates) and feces (32% of levonorgestrel and metabolites are excreted in the urine, mostly as glucuronide conjugates)	
Estradiol and norethindrone	Estradiol (oral): 53% Norethindrone (oral): 100%	Estradiol (oral): SHBG (37%), albumin (61%), and unbound (1 to 2 %) Norethindrone: SHBG (36%) and albumin (61%)	Estradiol (oral): liver (primary) Norethindrone: liver (primary)	Estradiol (oral): urine (metabolites as glucuronide and sulfate conjugates) Norethindrone (oral): liver (primary).	Estradiol (oral): 12 to 14/8 to 11 hours Norethindrone (transdermal): 2 to 3 hours
Estradiol and norgestimate	Not reported	Estradiol: primarily bound to SHBG and to albumin Norgestimate (17-deacetyl-norgestimate): primarily bound to serum proteins (99%)	Estradiol: liver (primary). Estradiol, estrone, and estriol are all active metabolites Norgestimate: liver (extensive) and gastrointestinal tract (extensive). 17-deacetylnorgestimate is an active metabolite	Estradiol: urine (estradiol, estrone, estriol, and glucuronide and sulfate conjugates) Norgestimate: urine and feces	Estradiol: 16 hours Norgestimate (17-deacetyl-norgestimate): 37 hours
Estrogens, conjugated and bazedoxifene	Bazedoxifene: 6% Estrogens, conjugated: Well absorbed	Bazedoxifene: 98 to 99% bound to plasma proteins Estrogens, conjugated: Primarily bound to SHBG and to albumin	Bazedoxifene: liver (extensive) via glucuronidation Estrogens, conjugated: liver (primary). Estradiol, estrone, and estriol are all active	Bazedoxifene: urine (<1%), feces (85%), and bile (major) Estrogens, conjugated: urine (estradiol, estrone, estriol, and glucuronide	Bazedoxifene: 30 hours Estrogens, conjugated: 17 hours

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
			metabolites	and sulfate conjugates)	
Estrogens, conjugated equine and medroxyprogesterone	Well absorbed	Estrogens, conjugated: largely bound to SHBG and albumin Medroxyprogesterone: primarily bound to plasma proteins (99%)	Estrogens, conjugated: liver (primary). Estradiol, estrone, and estriol are all active metabolites Medroxyprogesterone: liver (primary)	Estrogens, conjugated: urine (estradiol, estrone, estriol, and glucuronide and sulfate conjugates) Medroxyprogesterone: urine (most metabolites excreted as glucuronide conjugates with only minor amounts excreted as sulfates)	Estrogens, conjugated: (estrone): 20.7 to 23.6 hours Medroxyprogesterone: 26.2 to 46.3 hours
Ethinyl estradiol and norethindrone	Ethinyl estradiol: 55% Norethindrone: 64%	Ethinyl estradiol: largely bound to albumin (>95%) Norethindrone: largely bound to albumin and SHBG (>95%)	Ethinyl estradiol: liver (primary) Norethindrone acetate: liver (primary)	Ethinyl estradiol: urine and feces (primarily as metabolites) Norethindrone: urine and feces (primarily as metabolites)	Ethinyl estradiol: 24 hours Norethindrone: 13 hours

SHBG=sex hormone binding globulin

V. Drug Interactions

Major drug interactions with the estrogens are listed in Table 6.

Table 6. Major Drug Interactions with the Estrogens^{2-32,53}

Generic Name(s)	Interaction	Mechanism
Estrogens	CYP3A4 inducers or inhibitors	Inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (<i>Hypericum perforatum</i>) preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and result in side effects.

VI. Adverse Drug Events

The most common adverse drug events reported with the estrogens are listed in Tables 7 and 8. The boxed warning for the estrogens is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Estrogens-Single Entity Agents¹

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Conjugated, Synthetic B	Estrogens, Esterified*	Estropipate†
Breasts								
Breast cancer	-	-	✓	✓	✓ (injection)	-	✓	-
Enlargement	1.1 to 6.7 (Alora [®])	-	✓	✓	✓ (injection)	-	✓	✓
Fibrocystic breast changes	-	-	✓	✓	✓ (injection)	-	✓	-
Galactorrhea	-	-	✓	✓	✓ (injection)	-	✓	-
Neoplasm	1.1 to 5.6 (Alora [®])	-	-	-	-	-	-	-
Nipple discharge	-	-	✓	✓	✓ (injection)	-	✓	-
Nipple pain	1 to 7 (Evamist [®])	-	-	-	-	-	-	-
Pain	6.9 to 34.8 (Alora [®])/5.0 to 29.0 (Climara [®])/1.0 (Estring [®])/5.0 (Menostar [®])	-	✓	✓	✓ (injection)/ 7.0 to 11.0 (tablet)/ 2.1 to 4.9 (vaginal cream)	0 to 14	✓	-
Tenderness	2.5 to 8.8 (Divigel [®])/5.0 to 7.0 (Evamist [®])/6.5 to 12.9 (Minivelle [®] /Vivelle [®])/6.5 to 17.0 (Vivelle-Dot [®])	6.2 to 10.7 (vaginal ring)	✓	✓	✓ (injection)	-	✓	✓
Cardiovascular								
Cardiovascular	10 (Menostar [®])	-	-	-	-	-	-	-
Chest pain	1.1 to 4.5 (Alora [®])/1.0 to 3.0 (Estring [®])	-	-	-	-	-	-	-
Deep and superficial venous thrombosis	-	-	✓	✓	✓ (injection)	-	✓	-
Increase in blood pressure	0.0 to 6.7 (Alora [®])/0.0 to 2.9 (Minivelle [®] /Vivelle [®])/0.0 to 4.3 (Vivelle-Dot [®])	-	✓	✓	✓ (injection)	-	✓	-
Myocardial infarction	-	-	✓	✓	✓ (injection)	-	✓	-
Pulmonary embolism	-	-	✓	✓	✓ (injection)	-	✓	-
Stroke	-	-	✓	✓	✓ (injection)	-	✓	-
Syncope	1 to 3 (Estring [®])	-	-	-	-	-	-	-
Thrombophlebitis	-	-	✓	✓	✓ (injection)	-	✓	-
Vasodilation	0 to 6.7 (Alora [®])	-	-	-	2.8 to 2.9 (vaginal cream)	-	-	-
Central Nervous System								
Anxiety	0 to 10.0 (Alora [®])/1.0 to 3.0 (Estring [®])/0.0 to 3.8 (Minivelle [®] /Vivelle [®])/1.5 to 6.4 (Vivelle-Dot [®])	-	-	-	-	-	-	-
Asthenia	0 to 7.9 (Alora [®])	-	-	-	7 to 8 (tablet)	-	-	-
Chorea	-	-	✓	✓	-	-	✓	✓
Dementia	-	-	✓	✓	✓ (injection)	-	✓	-
Depression	1.1 to 3.4 (Alora [®])/1.0 to 8.0 (Climara [®])/0.0 to 6.8 (Minivelle [®] /Vivelle [®])/3.0 to 10.6 (Vivelle-Dot [®])	-	✓	✓	✓ (injection)/ 5 to 8 (tablet)	-	✓	✓
Dizziness	0.6 to 7.8 (Alora [®])/5.0 (Menostar [®])	-	✓	✓	✓ (injection)/ 4 to 6 (tablet)	1 to 7	✓	✓

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Conjugated, Synthetic B	Estrogens, Esterified*	Estropipate†
Exacerbation of chorea	-	-	-	-	✓ (injection)	-	-	-
Exacerbation of epilepsy	-	-	✓	✓	✓ (injection)	-	✓	-
Headache	5.6 to 21.3 (Alora®)/15.0 to 18.0 (Climara®)/13.0 (Estring®)/1.0 to 12.0 (Evamist®)/25.8 to 50.0 (Minivelle®/Vivelle®)/9.0 (Vagifem®)/14.9 to 50.0 (Vivelle-Dot®)	7.1 to 9.8 (vaginal ring)	✓	✓	✓ (injection)/26 to 32 (tablet)/2.1 to 3.5 (vaginal cream)	15 to 25	✓	✓
Hypesthesia	0 to 3.4 (Alora®)	-	-	-	-	-	-	-
Insomnia	1.1 to 4.6 (Alora®)/4.0 (Estring®)/1.5 to 4.6 (Minivelle®/Vivelle®)/1.5 to 6.4 (Vivelle-Dot®)	-	-	-	6 to 7 (tablet)	-	-	-
Irritability	-	-	✓	✓	-	-	✓	-
Migraine	0 to 6.7 (Alora®)/1.0 to 3.0 (Estring®)	-	✓	✓	✓ (injection)	-	✓	✓
Mood disturbances	-	-	✓	✓	-	-	✓	-
Nervousness	-	-	✓	✓	✓ (injection)/2 to 5 (tablet)	-	✓	-
Paresthesia	-	-	-	-	-	0 to 6	-	-
Possible growth potentiation of benign meningioma	-	-	-	-	✓ (injection)	-	-	-
Eyes								
Conjunctivitis	0 to 3.3 (Alora®)	-	-	-	-	-	-	-
Intolerance to contact lenses	-	-	✓	✓	✓ (injection)	-	✓	✓
Retinal vascular thrombosis	-	-	✓	✓	✓ (injection)	-	✓	-
Steepening of corneal curvature	-	-	✓	-	-	-	✓	✓
Gastrointestinal								
Abdominal cramps	-	-	✓	✓	✓ (injection)	-	✓	✓
Abdominal distention	-	2.7 to 7.1 (vaginal ring)	-	-	-	-	-	-
Abdominal pain	1.1 to 7.9 (Alora®)/0 to 16.0 (Climara®)/4.0 (Estring®)/8.0 (Menostar®)/7.0 (Vagifem®)	-	-	-	15 to 17 (tablet)	4 to 15	-	-
Bloating	-	-	✓	✓	✓ (injection)	-	✓	✓
Cholestatic jaundice	-	-	✓	✓	✓ (injection)	-	✓	✓
Constipation	1.1 to 6.7 (Alora®)/5.0 (Menostar®)/1.5 to 6.5 (Minivelle®/Vivelle®)/1.5 to 6.5 (Vivelle-Dot®)	-	-	-	-	-	-	-
Diarrhea	1.1 to 3.3 (Alora®)/1 to 3 (Estring®)/5 (Vagifem®)	-	-	-	6 to 7 (tablet)	-	-	-
Dyspepsia	1.1 to 9.0 (Alora®)/1.0 to 3.0 (Estring®)/5.0 (Menostar®)/0.0 to 9.2 (Minivelle®/Vivelle®)/2.9 to 9.2 (Vivelle-Dot®)	-	-	-	9 to 11 (tablet)	-	-	-
Enlargement of hepatic hemangiomas	-	-	✓	✓	✓ (injection)	-	✓	-
Flatulence	1.1 to 4.6 (Alora®)/1 to 7 (Climara®)/1 to 3 (Estring®)	-	-	-	6 to 7 (tablet)	4 to 7	-	-
Gastritis	1 to 3 (Estring®)	-	-	-	-	-	-	-
Gastroenteritis	0 to 4.4 (Alora®)	-	-	-	-	-	-	-
Increased incidence of gallbladder disease	-	-	✓	✓	✓ (injection)	-	✓	✓
Ischemic colitis	-	-	-	-	✓ (injection)	-	-	-

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Conjugated, Synthetic B	Estrogens, Esterified*	Estropipate†
Nausea	3.4 to 6.7 (Alora®)/1.0 to 6.0 (Climara®)/3.0 (Estring®)/1.0 to 3.0 (Evamist®)/0.0 to 6.2 (Minivelle®/Vivelle®)/3.9 to 6.2 (Vivelle-Dot®)	1.8 to 2.7 (vaginal ring)	✓	✓	✓ (injection)/6 to 9 (tablet)	7 to 12	✓	✓
Pancreatitis	-	-	✓	✓	✓ (injection)	-	✓	-
Vomiting	-	-	-	-	✓ (injection)	-	✓	✓
Genitourinary System								
Asymptomatic genital bacterial growth	4 (Estring®)	-	-	-	-	-	-	-
Breakthrough bleeding	-	-	✓	✓	-	-	-	✓
Cervical polyps	6 (Menostar®)	-	-	-	-	-	-	-
Change in amount of cervical secretion	-	-	✓	✓	-	-	-	✓
Changes in cervical ectropion	-	-	✓	✓	-	-	-	-
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow	-	-	✓	✓	-	-	-	✓
Cystitis	1 to 3 (Estring®)	-	-	-	-	-	-	-
Dysmenorrhea	0.0 to 6.5 (Minivelle®/Vivelle®)/0 to 6.5 (Vivelle-Dot®)	-	✓	✓	-	1 to 8	-	-
Dysuria	1 to 3 (Estring®)	-	-	-	1.4 (vaginal cream)	-	-	-
Endometrial cancer	-	-	✓	✓	-	-	-	-
Endometrial hyperplasia	-	-	✓	✓	-	-	-	-
Genital eruption	1 to 3 (Estring®)	-	-	-	-	-	-	-
Increase in size of uterine leiomyomata	-	-	✓	✓	-	-	-	✓
Intermenstrual bleeding	0.0 to 10.6 (Minivelle®/Vivelle®)/0 to 10.6 (Vivelle-Dot®)	8.0 to 9.8 (vaginal ring)	-	-	-	-	-	-
Leukorrhea	1.7 to 4.5 (Alora®)/1.0 to 7.0 (Climara®)/7.0 (Estring®)/11.0 (Menostar®)	-	-	-	4.0 to 7.0 (tablet)/2.1 to 2.9 (vaginal cream)	-	-	-
Metrorrhagia	4.1 to 9.6 (Divigel®)	-	-	-	-	-	-	-
Ovarian cancer	-	-	✓	✓	-	-	-	-
Spotting	-	-	✓	✓	-	-	-	✓
Urinary incontinence	1 to 3 (Estring®)	-	-	-	-	-	-	-
Urinary tract infection	1.7 to 5.6 (Alora®)/2.0 (Estring®)	0.9 to 3.6 (vaginal ring)	-	-	-	-	-	-
Urogenital pruritus	1 to 3 (Estring®)	-	-	-	-	-	-	-
Uterine pain	-	1.8 to 4.5 (vaginal ring)	-	-	-	-	-	-
Vaginal bleeding	8.7 to 33.3 (Alora®)	-	-	-	-	-	-	-
Vaginal candidiasis	-	6.2 to 10.7 (vaginal ring)	-	-	-	-	-	✓
Vaginal discharge	-	(vaginal ring)	-	-	-	-	-	-
Vaginal hemorrhage	4 (Estring®)	-	-	-	2.0 to 14.0 (tablet)/0.7 to 1.4 (vaginal cream)	-	-	-

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Conjugated, Synthetic B	Estrogens, Esterified*	Estropipate†
Vaginal irritation	-	0.9 to 1.8 (vaginal ring)	-	-	-	-	-	-
Vaginal moniliasis	-	-	-	-	5.0 to 6.0 (tablet)/1.4 (vaginal cream)	-	-	-
Vaginal mycosis	2.4 to 6.4 (Divigel®)	-	-	-	-	-	-	-
Vaginal pain/discomfort	5 (Estring®)	-	-	-	-	-	-	-
Vaginitis	0 to 8.0 (Alora®)/5.0 (Estring®)	-	-	-	5.0 to 7.0 (tablet)/1.4 to 2.1 (vaginal cream)	2 to 7	-	-
Vulvovaginal disorder	-	-	-	-	2.1 to 2.8 (vaginal cream)	-	-	-
Vulvovaginal mycotic infection	8 (Vagifem®)	-	-	-	-	-	-	-
Vulvovaginal pruritus	8 (Vagifem®)	-	-	-	-	-	-	-
Vulvovaginitis	-	0.9 to 5.3 (vaginal ring)	-	-	-	-	-	-
Respiratory								
Asthma	1.1 to 3.4 (Alora®)	-	-	-	-	-	-	-
Bronchitis	3.4 to 7.9 (Alora®)/1.0 to 3.0 (Estring®)/6.0 (Menostar®)	-	-	-	-	0 to 7	-	-
Cough increased	1.1 to 4.4 (Alora®)	-	-	-	4 to 7 (tablet)	-	-	-
Nasopharyngitis	4.1 to 5.7 (Divigel®)/1.0 to 5.0 (Evamist®)/8.3 to 19.6 (Minivelle®/Vivelle®)/6.4 to 19.6 (Vivelle-Dot®)	1.8 (vaginal ring)	-	-	-	-	-	-
Pharyngitis	2.2 to 4.5 (Alora®)/0.5 to 7.0 (Climara®)/1.0 (Estring®)	-	-	-	10 to 12 (tablet)	-	-	-
Pneumonia	0.6 to 4.5 (Alora®)	-	-	-	-	-	-	-
Respiratory infection	16.1 to 24.7 (Alora®)	-	-	-	-	-	-	-
Rhinitis	2 to 6 (Climara®)	-	-	-	6 to 10 (tablet)	4 to 7	-	-
Sinus congestion	2.9 to 6.5 (Minivelle®/Vivelle®)/0 to 6.5 (Vivelle-Dot®)	-	-	-	-	-	-	-
Sinusitis	6.7 to 12.2 (Alora®)/4.0 to 5.0 (Climara®)/4.0 (Estring®)/5.3 to 13.1 (Minivelle®/Vivelle®)/5.3 to 13.1 (Vivelle-Dot®)	1.8 to 3.6 (vaginal ring)	-	-	6 to 11 (tablet)	3 to 7	-	-
Upper respiratory tract infection	6.0 to 17.0 (Climara®)/1.6 to 5.7 (Divigel®)/5.0 (Estring®)/16.0 (Menostar®)/5.0 (Vagifem®)/4.5 to 10.7 (Minivelle®/Vivelle®)/4.5 to 10.7 (Vivelle-Dot®)	3.6 to 4.4 (vaginal ring)	-	-	9 to 12 (tablet)	-	-	-
Skin								
Acne	-	-	-	-	1.4 (vaginal cream)	-	-	-
Application site reaction	5.7 to 56.7 (Alora®)/9.0 (Menostar®)	-	-	-	-	-	-	-
Chloasma or melasma that may persist when drug is discontinued	-	-	✓	✓	✓ (injection)	-	✓	✓
Cyst	0 to 6.7 (Alora®)	-	-	-	-	-	-	-
Dermatitis	1 to 3 (Estring®)	-	-	-	-	-	-	-
Erythema multiforme	-	-	✓	✓	✓ (injection)	-	✓	✓
Erythema nodosum	-	-	✓	✓	✓ (injection)	-	✓	✓

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Conjugated, Synthetic B	Estrogens, Esterified*	Estropipate†
Hemorrhagic eruption	-	-	✓	✓	✓ (injection)	-	✓	✓
Hemorrhoids	1 to 3 (Estring®)	-	-	-	-	-	-	-
Hirsutism	0.6 to 4.5 (Alora®)	-	✓	✓	✓ (injection)	-	✓	✓
Loss of scalp hair	-	-	✓	✓	✓ (injection)	-	✓	✓
Pruritus	1.1 to 6.7 (Alora®)/0.5 to 6.0 (Climara®)	-	✓	✓	✓ (injection)/ 4.0 to 5.0 (tablet)/ 0.7 to 1.4 (vaginal cream)	-	✓	-
Rash	2.9 to 8.9 (Alora®)	-	✓	✓	✓ (injection)	-	✓	-
Skin hypertrophy	1 to 3 (Estring®)	-	-	-	-	-	-	-
Other								
Accidental injury	4.5 to 8.9 (Alora®)/14.0 (Menostar®)	-	-	-	6 to 12 (tablet)	3 to 8	-	-
Aggravation of porphyria	-	-	✓	✓	✓ (injection)	-	✓	✓
Allergy	1 (Estring®)	-	-	-	-	-	-	-
Allergic reaction	0.6 to 4.5 (Alora®)	-	-	-	-	-	-	-
Anaphylactoid/ anaphylactic reactions	-	-	✓	✓	✓ (injection)	-	✓	-
Angioedema	-	-	✓	✓	✓ (injection)	-	✓	-
Arthralgia	1.1 to 12.4 (Alora®)/1.0 to 5.0 (Climara®)/3.0 (Estring®)/1.0 to 4.0 (Evamist®)/12.0 (Menostar®)/3.8 to 8.5 (Minivelle®/Vivelle®)/3.8 to 8.5 (Vivelle-Dot®)	1.8 (vaginal ring)	✓	✓	✓ (injection)/ 7 to 14 (tablet)	-	✓	-
Arthritis	4 (Estring®)/5 (Menostar®)	-	-	-	-	-	-	-
Back pain	3.3 to 7.9 (Alora®)/4.0 to 9.0 (Climara®)/6.0 (Estring®)/3.0 to 5.0 (Evamist®)/7.7 to 10.6 (Minivelle®/Vivelle®)/7.0 (Vagifem®)/7.7 to 10.6 (Vivelle-Dot®)	3.6 to 6.2 (vaginal ring)	-	-	13 to 14 (tablet)	-	-	-
Bone fracture spontaneous	0 to 3.3 (Alora®)	-	-	-	-	-	-	-
Changes in libido	-	-	✓	✓	✓ (injection)	-	✓	✓
Changes in weight	-	-	✓	✓	✓ (injection)	-	✓	✓
Edema	0.5 to 13.0 (Climara®)	-	✓	✓	✓ (injection)	-	✓	✓
Exacerbation of asthma	-	-	✓	✓	✓ (injection)	-	✓	-
Family stress	2 (Estring®)	-	-	-	-	-	-	-
Fever	-	-	-	-	-	-	-	-
Flu syndrome	3.4 to 13.3 (Alora®)/3.0 (Estring®)/0.0 to 7.8 (Minivelle®/Vivelle®)	-	-	-	10 to 11 (tablet)	4 to 7	-	-
Fungal infection	0 to 10.0 (Alora®)	-	-	-	-	-	-	-
Genital disorder	-	2.7 (vaginal ring)	-	-	-	-	-	-
Glucose intolerance	-	-	-	-	✓ (injection)	-	-	-
Hot flashes	2 (Estring®)/0.0 to 2.9 (Minivelle®/Vivelle®)/0 to 6.4 (Vivelle-Dot®)	-	-	-	-	-	-	-
Hypocalcemia	-	-	✓	✓	✓ (injection)	-	✓	-
Increased triglycerides	-	-	✓	✓	✓ (injection)	-	✓	-
Increased weight	0.6 to 4.5 (Alora®)/0.0 to 4.3 (Minivelle®/Vivelle®)/1.9 to 8.5 (Vivelle-Dot®)	-	-	-	-	-	-	-
Infection	1.1 to 3.4 (Alora®)/5.0 (Menostar®)	-	-	-	18 to 23 (tablet)	-	-	-

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Conjugated, Synthetic B	Estrogens, Esterified*	Estropipate†
Influenza	0.0 to 7.6 (Minivelle®/Vivelle®)/2.3 to 8.5 (Vivelle-Dot®)	-	-	-	-	-	-	-
Injection site edema	-	-	-	-	✓ (injection)	-	-	-
Injection site pain	-	-	-	-	✓ (injection)	-	-	-
Injection site phlebitis	-	-	-	-	✓ (injection)	-	-	-
Joint disorder	1.1 to 4.5 (Alora®)	-	-	-	-	-	-	-
Leg cramps	-	-	✓	✓	✓ (injection)/ 3 to 7 (tablet)	-	✓	-
Leg edema	1 to 3 (Estring®)	-	-	-	-	-	-	-
Metabolic and nutritional disorders	12 (Menostar®)	-	-	-	-	-	-	-
Moniliasis	6 (Estring®)/5 (Vagifem®)	-	-	-	0.7 to 1.4 (vaginal cream)	-	-	-
Muscle cramp	-	-	-	-	1.4 (vaginal cream)	-	-	-
Myalgia	1.7 to 5.6 (Alora®)/5.0 (Menostar®)	-	-	-	5 to 9 (tablet)	-	-	-
Neck pain	0.0 to 4.5 (Minivelle®/Vivelle®)/3.1 to 6.4 (Vivelle-Dot®)	-	-	-	-	-	-	-
Otitis media	0 to 3.4 (Alora®)/1.0 to 3.0 (Estring®)	-	-	-	-	-	-	-
Pain	5.6 to 10.1 (Alora®)/1.0 to 11.0 (Climara®)/13.0 (Menostar®)/0.0 to 6.2 (Minivelle®/Vivelle®)/4.3 to 6.2 (Vivelle-Dot®)	-	-	-	17.0 to 20.0 (tablet)/0.7 to 1.4 (vaginal cream)	10 to 19	-	-
Pain in limb	4.3 to 7.7 (Minivelle®/Vivelle®)/4.3 to 7.7 (Vivelle-Dot®)	0.9 to 2.7 (vaginal ring)	-	-	-	-	-	-
Pelvic pain	-	-	-	-	2.8 to 2.9 (vaginal cream)	-	-	-
Peripheral edema	1.7 to 4.4 (Alora®)	-	-	-	-	-	-	-
Reduced carbohydrate tolerance	-	-	✓	✓	-	-	✓	✓
Sinus headache	1.5 to 10.9 (Minivelle®/Vivelle®)/1.5 to 10.9 (Vivelle-Dot®)	-	-	-	-	-	-	-
Skeletal pain	2 (Estring®)	-	-	-	-	-	-	-
Tooth disorder	1 to 3 (Estring®)	-	-	-	-	-	-	-
Toothache	1 to 3 (Estring®)	-	-	-	-	-	-	-
Urticaria	-	-	✓	✓	✓ (injection)	-	✓	-

*Adverse events have been reported with estrogen and/or progestin therapy (estrogens, conjugated equine injection formulation only).

†Adverse events have been reported with estrogen therapy.

-Incidence not reported or <1%

✓ Incidence not specified.

Table 8. Adverse Drug Events (%) for the Estrogens-Combination Products²⁶⁻³⁵

Adverse Event	Estradiol and Drospirenone	Estradiol and Levonorgestrel	Estradiol and Norethindrone	Estradiol and Norgestimate	Estrogens, Conjugated and Bazedoxifene	Estrogens, Conjugated Equine and Medroxyprogesterone	Ethinyl Estradiol and Norethindrone
Abdominal pain	-	4.2	6 to 14*	-	7	13 to 23	5.3 to 10.2
Accidental injury	-	3.3	3 to 17	-	-	4 to 10	-
Acne	-	-	4 to 5*	-	-	-	-
Anxiety	-	-	-	-	-	2 to 5	-
Application site reaction	-	40.6	2 to 23*	-	-	-	-
Arthralgia	-	4.2	6*	9	-	7 to 13	2.9 to 5.8
Asthenia	-	-	8 to 13*	-	-	6 to 10	-
Back pain	-	6.1	3 to 15	12	-	13 to 16	4.7 to 5.3
Breast enlargement	-	-	2 to 7*	-	-	2 to 5	-
Breast pain or discomfort	3.3 to 17.9	18.9	17 to 48	16	-	12 to 38	5.3 to 9.0
Bronchitis	-	4.2	3 to 5*	-	-	-	-
Cervical polyp	1.2	-	-	-	-	-	-
Cervix disorder	-	-	-	-	-	4 to 5	-
Constipation	-	-	2 to 5*	-	-	-	-
Cough	-	-	-	5	-	5 to 8	-
Depression	-	5.7	3 to 9*	5	-	5 to 11	3.7 to 5.8
Diarrhea	2.2	-	4 to 14	-	8	5 to 7	3.9 to 5.7
Dizziness	-	-	6 to 7*	5	5	3 to 5	-
Dysmenorrhea	-	-	20 to 31*	8	-	3 to 13	-
Dyspepsia	-	-	1 to 8*	-	7	5 to 8	3.1 to 5.3
Edema	-	3.8	-	-	-	-	15.7 to 16.9
Emotional lability	1.2	-	0 to 6†	-	-	-	-
Endometrial thickening	-	-	10†	-	-	-	-
Fatigue	-	-	-	6	-	-	-
Female genital tract bleeding	14	-	-	-	-	-	-
Flatulence	-	3.8	4 to 7*	5	-	5 to 9	-
Gastroenteritis	-	-	0 to 6†	-	-	-	-
Gastrointestinal and abdominal pains	6.0 to 6.5	-	-	12	-	-	-
Headache	6	5.2	11 to 25	23	-	28 to 37	5.7 to 18.2
Hypertension	-	3.3	-	-	-	-	-
Hypertonia	-	-	-	-	-	3 to 4	-
Infection	-	3.3	3 to 5*	-	-	16 to 21	-
Influenza-like symptoms	-	4.7	5 to 9*	11	-	8 to 12	-
Insomnia	-	-	0 to 8	-	-	6 to 7	-

Adverse Event	Estradiol and Drospirenone	Estradiol and Levonorgestrel	Estradiol and Norethindrone	Estradiol and Norgestimate	Estrogens, Conjugated and Bazedoxifene	Estrogens, Conjugated Equine and Medroxyprogesterone	Ethinyl Estradiol and Norethindrone
Leg cramps	-	-	-	-	-	3 to 7	-
Leukorrhea	-	-	5 to 10*	-	-	3 to 9	-
Menorrhagia	-	-	2 to 5*	-	-	-	-
Menstrual disorder	-	-	6 to 19*	-	-	-	-
Migraine	1	-	-	-	-	-	-
Moniliasis, genital	-	-	0 to 6†	-	-	4 to 8	-
Muscle spasms	-	-	-	-	9	-	-
Myalgia	-	-	-	5	-	4 to 5	7.8 to 8.6
Nasopharyngitis	-	-	21†	-	-	-	-
Nausea	3.3	-	3 to 12	6	8	7 to 11	5.3 to 33.0
Neck pain	-	-	-	-	5	-	-
Nervousness	-	-	3 to 6*	-	-	2 to 3	1.6 to 5.4
Oropharyngeal pain	-	-	-	-	7	-	-
Ovarian cyst	-	-	0 to 7†	-	-	-	-
Pain	-	5.2	4 to 19*	6	-	11 to 20	-
Pain in extremity	-	-	5†	-	-	-	-
Papanicolaou smear suspicious	-	-	4 to 8*	-	-	-	-
Pelvic pain	-	-	-	-	-	4 to 5	-
Peripheral edema	2.2	-	6*	-	-	3 to 4	-
Pharyngitis	-	-	4 to 10*	7	-	8 to 13	-
Post-menopausal bleeding	-	-	5 to 11†	-	-	-	-
Pruritus	-	-	-	-	-	4 to 10	-
Rash	-	2.4	5 to 6*	-	-	4 to 6	-
Respiratory disorder	-	-	7 to 13*	-	-	-	-
Rhinitis	-	-	7 to 22*	-	-	6 to 10	12.7 to 15.1
Sinusitis	-	3.8	4 to 15	8	-	7 to 10	8.1 to 9.4
Tooth disorder	-	-	4 to 6*	5	-	-	-
Upper respiratory tract infection	-	13.2	10 to 18†	21	-	9 to 11	-
Urinary tract infection	-	3.3	-	-	-	-	3.7 to 6.2
Uterine fibroid	-	-	0 to 5†	-	-	-	-
Vaginal bleeding	9	36.8	-	-	-	-	-
Vaginal hemorrhage	-	-	3 to 26	-	-	1 to 6	-
Vaginitis	-	1.9	6 to 13*	7	-	4 to 7	5.4 to 4.5
Viral infection	-	-	0 to 6†	6	-	-	7.0 to 8.6

Adverse Event	Estradiol and Drospirenone	Estradiol and Levonorgestrel	Estradiol and Norethindrone	Estradiol and Norgestimate	Estrogens, Conjugated and Bazedoxifene	Estrogens, Conjugated Equine and Medroxyprogesterone	Ethinyl Estradiol and Norethindrone
Vomiting	-	-	-	-	-	-	5.3 to 33.0
Vulvovaginal fungal infections	5.5	-	-	-	-	-	-
Weight increase	-	2.8	0 to 9†	-	-	-	-

*Transdermal patch only.

†Oral therapy only.

-Incidence not reported or <1.0%

✓ Incidence not specified.

Table 9. Boxed Warning for the Estrogens⁵³

WARNING
<p><u>Estrogen-alone therapy:</u> Endometrial cancer: There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.</p> <p>Cardiovascular disorders and probable dementia: Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens 0.625 mg alone, relative to placebo.</p> <p>The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years or older during 5.2 years of treatment with daily CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.</p> <p>In the absence of comparable data, these risks should be assumed to be similar for other doses of conjugated estrogens and other dosage forms of estrogens. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.</p> <p><u>Estrogen plus progestin therapy:</u> Cardiovascular disorders and probable dementia: Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogen 0.625 mg combined with medroxyprogesterone 2.5 mg, relative to placebo. The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years or older during 4 years of treatment with daily conjugated estrogen 0.625 mg combined with medroxyprogesterone 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.</p> <p>Breast cancer: The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. In the absence of comparable data, these risks should be assumed to be similar for other doses of conjugated estrogen and medroxyprogesterone, and other combinations and dosage forms of estrogens and progestins. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.</p>

VII. Dosing and Administration

The usual dosing regimens for the estrogens are listed in Table 10.

Table 10. Usual Dosing Regimens for the Estrogens^{2-32,53}

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Estradiol	<u>Palliative treatment of advanced androgen-dependent carcinoma of the prostate:</u> Tablet (Estrace®): 1 to 2 mg TID <u>Palliative treatment of breast cancer in appropriately selected women and men with metastatic breast cancer:</u>	Safety and efficacy in children have not been established.	Tablet (Estrace®): 0.5 mg 1 mg 2 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p>Tablet (Estrace®): 10 mg TID for ≥3 months</p> <p><u>Prevention of postmenopausal osteoporosis:</u> Tablet (Estrace®): initial, 0.5 mg/day; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Alora®): initial, 0.025 mg/day applied twice weekly; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Menostar®): 14 µg/day applied once weekly</p> <p>Transdermal patch (Vivelle-Dot®, Minivelle®): initial, 0.025 mg/day applied twice weekly; maintenance, adjust dose as necessary</p> <p><u>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:</u> Tablet (Estrace®): initial, 1 to 2 mg/day; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Alora®): initial, 0.05 mg/day applied twice weekly; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Vivelle-Dot®, Minivelle®): initial, 0.025 mg/day applied twice weekly; maintenance, adjust dose as necessary</p> <p><u>Treatment of moderate to severe vasomotor symptoms associated with menopause:</u> Tablet (Estrace®): initial, 1 to 2 mg/day administered cyclically (three weeks on and one week off); maintenance, adjust dose as necessary</p> <p>Transdermal gel (Divigel®): initial, 0.25 g/day; maintenance, adjust dose as necessary</p> <p>Transdermal gel (Elestrin®): initial, 0.87 g/day (one pump); maintenance, adjust dose as necessary</p> <p>Transdermal patch (Alora®): initial, 0.05 mg/day applied twice weekly; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Climara®): initial, 0.025 mg/day</p>		<p>Transdermal gel (Divigel®): 0.25 mg (0.1%) 0.5 mg (0.1%) 1 mg (0.1%)</p> <p>Transdermal gel (Elestrin®): 0.87 gm/pump (0.06%)</p> <p>Transdermal patch (Alora®): 0.025 mg/day 0.05 mg/day 0.075 mg/day 0.1 mg/day</p> <p>Transdermal patch (Climara®): 0.025 mg/day 0.0375 mg/day 0.05 mg/day 0.06 mg/day 0.075 mg/day 0.1 mg/day</p> <p>Transdermal patch (Menostar®): 14 µg/day</p> <p>Transdermal patch (Minivelle®): 0.025 mg/day 0.0375 mg/day 0.05 mg/day 0.075 mg/day 0.1 mg/day</p> <p>Transdermal patch (Vivelle-Dot®): 0.025 mg/day 0.0375 mg/day 0.05 mg/day 0.075 mg/day 0.1 mg/day</p> <p>Transdermal spray (Evamist®): 1.53 mg/spray</p>

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p>applied once weekly; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Vivelle-Dot[®], Minivelle[®]): initial, 0.0375 mg/day applied twice weekly; maintenance, adjust dose as necessary</p> <p>Transdermal spray (Evamist[®]): initial, one spray daily; maintenance, adjust dose as necessary</p> <p><u>Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause:</u> Tablet (Estrace[®]): initial, 1 to 2 mg/day administered cyclically (three weeks on and one week off); maintenance, adjust dose as necessary</p> <p>Transdermal patch (Alora[®]): initial, 0.05 mg/day applied twice weekly; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Climara[®]): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary</p> <p>Transdermal patch (Vivelle-Dot[®], Minivelle[®]): initial, 0.0375 mg/day applied twice weekly; maintenance, adjust dose as necessary</p> <p><u>Treatment of atrophic vaginitis due to menopause:</u> Vaginal tablet (Vagifem[®]): one tablet administered intravaginally for two weeks, followed by one tablet intravaginally twice weekly; in general start treatment with 10 µg</p> <p><u>Treatment of moderate to severe urogenital symptoms due to postmenopausal atrophy of the vagina and/or the lower urinary tract:</u> Vaginal ring (Estring[®]): 2 mg vaginal ring inserted as deeply as possible into the upper one-third of the vaginal vault; the ring is to remain in place continuously for three months</p> <p><u>Treatment of vulvar and vaginal atrophy:</u> Vaginal cream (Estrace[®]): 2 to 4 g/day administered intravaginally for one to two weeks, followed by ½ the initial dose for a similar period; maintenance, 1 g administered intravaginally one to three times per week (may be used after restoration of the vaginal mucosa has been achieved)</p>		<p>(1.7%)</p> <p>Vaginal cream (Estrace[®]): 0.1 mg/g (0.01%)</p> <p>Vaginal ring (Estring[®]): 2 mg (7.5 µg/day)</p> <p>Vaginal tablet (Vagifem[®]): 10 µg</p>
Estradiol acetate	<p><u>Treatment of moderate to severe vasomotor symptoms associated with menopause:</u> Vaginal ring: initial, 0.05 mg/day; maintenance, 0.05 to 0.1 mg/day</p> <p><u>Treatment of moderate to severe vulvar and vaginal</u></p>	Safety and efficacy in children have not been established.	Vaginal ring (Femring [®]): 0.05 mg/day 0.1 mg/day

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<u>atrophy associated with menopause:</u> Vaginal ring: initial, 0.05 mg/day; maintenance, 0.05 to 0.1 mg/day		
Estradiol cypionate	<u>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:</u> Injection: 1.5 to 2 mg intramuscularly at monthly intervals <u>Treatment of vasomotor symptoms associated with menopause:</u> Injection: 1 to 5 mg intramuscularly every three to four weeks	Safety and efficacy in children have not been established.	Injection (intramuscular): 5 mg/mL
Estradiol valerate	<u>Palliative treatment of advanced prostate cancer:</u> Injection: 30 mg or more intramuscularly every one to two weeks <u>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:</u> Injection: 10 to 20 mg intramuscularly every four weeks <u>Treatment of vasomotor symptoms associated with menopause:</u> Injection: 10 to 20 mg intramuscularly every four weeks <u>Treatment of vulvar and vaginal atrophy associated with menopause:</u> Injection: 10 to 20 mg intramuscularly every four weeks	Safety and efficacy in children have not been established.	Injection (intramuscular): 10 mg/mL 20 mg/mL 40 mg/mL
Estrogens, conjugated equine	<u>Palliative treatment of advanced androgen-dependent carcinoma of the prostate:</u> Tablet: 1.25 to 2.5 mg TID <u>Palliative treatment of breast cancer in appropriately selected women and men with metastatic disease:</u> Tablet: 10 mg TID for ≥ 3 months <u>Prevention of postmenopausal osteoporosis:</u> Tablet: initial, 0.3 mg/day; maintenance, subsequent dosage adjustment may be made based upon the individual clinical and bone mineral density responses <u>Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology:</u> Injection: 25 mg intramuscularly or intravenously once; repeat in six to 12 hours if necessary <u>Treatment of atrophic vaginitis and kraurosis vulvae:</u> Vaginal cream: initial, 0.5 g/day intravaginally administered cyclically (three weeks on and one week off); maintenance, 0.5 to 2 g	Safety and efficacy in children have not been established.	Injection (intramuscular and intravenous): 25 mg Tablet: 0.3 mg 0.45 mg 0.625 mg 0.9 mg 1.25 mg Vaginal cream: 0.625 mg/g (30 or 42.5 g)

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p><u>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:</u> Tablet: 0.3 or 0.625 mg/day administered cyclically (three weeks on and one week off); maintenance, doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium</p> <p><u>Treatment of moderate to severe vasomotor symptoms associated with menopause:</u> Tablet: initial, 0.3 mg/day; maintenance, subsequent dosage adjustment may be made based upon the individual patient response</p> <p><u>Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause:</u> Vaginal cream: 0.5 mg/day intravaginally in a twice-weekly continuous regimen or in a cyclic regimen of 21 days of therapy followed by seven days off of therapy</p> <p><u>Treatment of moderate to severe vaginal dryness symptoms of vulvar and vaginal atrophy associated with menopause:</u> Tablet: initial, 0.3 mg/day; maintenance, subsequent dosage adjustment may be made based upon the individual patient response</p>		
Estrogens, conjugated, synthetic B	<p><u>Treatment of moderate to severe vasomotor symptoms associated with menopause:</u> Tablet: 0.3 to 1.25 mg/day</p> <p><u>Treatment of moderate to severe vaginal dryness and pain with intercourse, symptoms of vulvar and vaginal atrophy, associated with menopause:</u> Tablet: 0.3 mg/day</p>	Safety and efficacy in children have not been established.	Tablet: 0.3 mg 0.45 mg
Estrogens, esterified	<p><u>Palliative treatment of breast cancer in appropriately selected women and men with metastatic disease:</u> Tablet: 10 mg TID for ≥ 3 months</p> <p><u>Palliative therapy of advanced prostatic carcinoma:</u> Tablet: 1.25 to 2.5 mg TID</p> <p><u>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:</u> Tablet (hypogonadism): 2.5 to 7.5 mg/day, in divided doses for 20 days, followed by a rest period of 10 days' duration</p> <p>Tablet (female castration, primary ovarian failure): 1.25 mg/day administered cyclically (three weeks on and one week off)</p> <p><u>Treatment of moderate to severe vasomotor symptoms associated with menopause:</u> Tablet: 1.25 mg/day administered cyclically (three</p>	Safety and efficacy in children have not been established.	Tablet: 0.3 mg 0.625 mg 1.25 mg 2.5 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p>weeks on and one week off)</p> <p><u>Treatment of vulval and vaginal atrophy associated with menopause:</u> Tablet: 0.3 to 1.25 mg or more daily administered cyclically (three weeks on and one week off)</p>		
Estropipate	<p><u>Prevention of osteoporosis:</u> Tablet: 0.75 mg/day for 25 days of a 31-day cycle per month</p> <p><u>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:</u> Tablet : 1.5 to 9 mg/day for the first three weeks of a theoretical cycle, followed by a rest period of eight to 10 days</p> <p><u>Treatment of moderate to severe vasomotor symptoms associated with menopause and treatment of vulval and vaginal atrophy:</u> Tablet: 0.75 to 6 mg/day</p>	Safety and efficacy in children have not been established.	Tablet: 0.75 mg 1.5 mg 3 mg
Combination Products			
Estradiol and drospirenone	<p><u>Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause:</u> Tablet: 0.5-0.25 mg or 1-0.5 mg QD</p> <p><u>Treatment of moderate to severe vasomotor symptoms due to menopause:</u> Tablet: 1-0.5 mg QD</p>	Safety and efficacy in children have not been established.	Tablet*: 0.5-0.25 mg 1.0-0.5 mg
Estradiol and levonorgestrel	<p><u>Prevention of postmenopausal osteoporosis and treatment of moderate to severe vasomotor symptoms due to menopause:</u> Transdermal patch: 0.045-0.015 mg transdermal patch worn continuously for seven days; maintenance, a new 0.045-0.015 mg transdermal patch should be applied weekly during a 28-day cycle</p>	Safety and efficacy in children have not been established.	Transdermal patch: 0.045-0.015 mg/day
Estradiol and norethindrone	<p><u>Prevention of postmenopausal osteoporosis:</u> Tablet: 0.5-0.1 or 1-0.5 mg QD</p> <p><u>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:</u> Transdermal patch: 0.05-0.014 or 0.05-0.25 mg transdermal patch worn continuously; maintenance, a new 0.05-0.014 or 0.05-0.25 mg transdermal system should be applied twice weekly during a 28-day cycle†</p> <p><u>Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause:</u> Tablet: 1-0.5 mg QD</p> <p>Transdermal patch: 0.05-0.014 or 0.05-0.25 mg transdermal patch worn continuously; maintenance, a new 0.05-0.014 or 0.05-0.25 mg transdermal system should be applied twice weekly during a 28-day cycle†</p>	Safety and efficacy in children have not been established.	Tablet‡: 0.5-0.1 mg 1.0-0.5 mg Transdermal patch: 0.05-0.14 mg 0.05-0.25 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p><u>Treatment of moderate to severe vasomotor symptoms due to menopause:</u> Tablet: 0.5-0.1 or 1-0.5 mg QD</p> <p>Transdermal patch: 0.05-0.014 or 0.05-0.25 mg transdermal patch worn continuously; maintenance, a new 0.05-0.014 or 0.05-0.25 mg transdermal system should be applied twice weekly during a 28-day cycle†</p>		
Estradiol and norgestimate	<p><u>Prevention of postmenopausal osteoporosis, treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, and treatment of moderate to severe vasomotor symptoms due to menopause:</u> Tablet: one tablet QD</p>	Safety and efficacy in children have not been established.	Tablet‡: 1 mg (estradiol) and 1-0.09 mg (estradiol/norgestimate)
Estrogens, conjugated and bazedoxifene	<p><u>Prevention of postmenopausal osteoporosis and treatment of moderate to severe vasomotor symptoms due to menopause:</u> Tablet: one tablet QD</p>	Safety and efficacy in children have not been established.	Tablet: 0.45-20 mg
Estrogens, conjugated equine and medroxy-progesterone	<p><u>Prevention of postmenopausal osteoporosis, treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, and treatment of moderate to severe vasomotor symptoms due to menopause:</u> Tablet: one tablet QD</p>	Safety and efficacy in children have not been established.	Tablet : 0.3-1.5 mg (Prempro®) 0.45-1.5 mg (Prempro®) 0.625-2.5 mg (Prempro®) 0.625-5 mg (Prempro®) 0.625 mg (estrogen, conjugated equine) and 0.625-5 mg (estrogen, conjugated equine/medroxy-progesterone) (Premphase®)
Ethinyl estradiol and norethindrone	<p><u>Prevention of postmenopausal osteoporosis and treatment of moderate to severe vasomotor symptoms due to menopause:</u> Tablet: one tablet QD</p>	Safety and efficacy in children have not been established.	Tablet#: 2.5 µg-0.5 mg 5 µg-1 mg

QD=once daily, TID=three times daily

*Available in three blisters of 28 tablets.

†Can also be administered in combination with an estradiol transdermal patch. With this regimen, estradiol transdermal patch (0.05 mg) is administered for the first 14 days of a 28-day cycle, followed by estradiol/norethindrone 0.05/0.14 or 0.05/0.25 mg transdermal patch for the remaining 14 days of the 28-day cycle.

‡Activella®: available as 28 tablets in a calendar dial pack dispenser.

§Available in cartons of six pouches. Each pouch consists of a blister card containing three 1 mg estradiol tablets followed by three 1.0/0.9 mg estradiol/norgestimate tablets. The pattern of three estradiol tablets and three combination tablets repeats for a total of 30 tablets per blister card. Each blister card contains 15 tablets of each of the two tablets. The three day phases are alternated continuously during treatment.

|| Prempro®: available as one or three blisters of 28 tablets. Premphase®: available as one blister of 28 tablets.

#Femhrt®: available as bottles of 90 tablets or blisters of 28 tablets.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the estrogens are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Estrogens

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Comparative Trials of Estrogens				
WHI Steering Committee ⁴⁸ (2004) WHI CEE 0.625 mg once daily vs placebo	DB, MC, PC, RCT Postmenopausal women, 50 to 79 years of age, with prior hysterectomy	N=10,739 6.8 years (mean duration of follow-up)	Primary: Rate of CHD (nonfatal MI or CHD death), invasive breast cancer Secondary: Stroke, PE, colorectal cancer, hip fracture, and deaths from other causes	Primary: Treatment with CEE did not significantly affect the incidence of CHD or overall mortality. The estimated HR for CHD was 0.91 (95% CI, 0.75 to 1.12), breast cancer was 0.77 (95% CI, 0.59 to 1.01), and death was 1.04 (95% CI, 0.88 to 1.22). There was an estimated 7 fewer cases of breast cancer among the women treated with CEE compared to the women taking placebo, but that did not reach statistical significance. Secondary: Treatment with CEE increased the risk of stroke and reduced the risk of hip and other fractures. The estimated HR for breast cancer was 0.77 (95% CI, 0.59 to 1.01), stroke was 1.39 (95% CI, 1.10 to 1.77), PE was 1.34 (95% CI, 0.87 to 2.06), colorectal cancer was 1.08 (95% CI, 0.75 to 1.55), hip fracture was 0.61 (95% CI, 0.41 to 0.91), and global index was 1.01 (95% CI, 0.91 to 1.12). Thus, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10,000 person-years.
Stefanick et al. ⁵⁴ (2006) WHI CEE 0.625 mg vs placebo	DB, MC, PC, RCT Postmenopausal women, 50 to 79 years of age, with prior hysterectomy	N=10,739 7.1 years (mean duration of follow-up)	Primary: Breast cancer incidence, tumor characteristics, mammogram findings Secondary: Not reported	Primary: Treatment with CEE did not increase the risk of breast cancer compared to placebo. The HR for invasive breast cancer was 0.80 (95% CI, 0.62 to 1.04; P=0.09) and 0.82 (95% CI, 0.65 to 1.04; P=0.10) for total breast cancer. However, breast cancer that developed in patients who had received CEE was associated with larger tumor size (P=0.03) and higher percentage of positive nodes (P=0.07) compared to placebo. The risk of invasive breast cancer was significantly lower in women who had no prior hormone use. The HR was 0.65 (95% CI, 0.46 to 0.92) for women with no prior hormone use and 1.02 (95% CI, 0.70 to 1.50) for women with prior hormone use (P=0.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>There were larger numbers of mammograms with abnormalities that required primarily short interval follow-ups in the CEE group compared to placebo (P<0.001).</p> <p>Secondary: Not reported</p>
<p>Hsia et al.⁵⁵ (2006) WHI CEE 0.625 mg once daily vs placebo</p>	<p>DB, MC, PC, RCT Postmenopausal women 50 to 79 years of age at baseline, who had undergone prior hysterectomy</p>	<p>N=10,739 7.1 years (mean duration of follow-up)</p>	<p>Primary: CHD events (MI or coronary death) Secondary: CABG or PCI, angina, hospitalized CHF, acute coronary syndrome</p>	<p>Primary: There were 201 CHD events reported among the women assigned to estrogen treatment compared to 217 events in the placebo group (HR, 0.95; 95% CI, 0.79 to 1.16).</p> <p>The HR was 0.61 (95% CI, 0.25 to 1.50) for the 50 to 59 years age group, 0.86 (95% CI, 0.60 to 1.25) for the 60 to 69 years age group, and 1.10 (95% CI, 0.69 to 1.73) for the 70 to 79 years of age group; P=0.35.</p> <p>There was no significant trend in risk of primary outcome over time (P=0.14).</p> <p>Secondary: Coronary revascularization was less frequent among the 50 to 59 years age group that was assigned to estrogen treatment (HR, 0.55; 95% CI, 0.35 to 0.86). Composite outcomes were less frequent with estrogen treatment in this age group (HR, 0.66; 95% CI, 0.45 to 0.96).</p> <p>There were no differences in secondary coronary outcomes between treatment groups in the women 60 to 69 years of age or women 70 to 79 years of age.</p>
<p>Chlebowski et al.⁵⁶ (2016) WHI CEE 0.625 mg once daily plus medroxyprogesterone acetate 2.5mg once daily (as a</p>	<p>DB, MC, PC, RCT Postmenopausal women 50 to 79 years of age at baseline, with an intact uterus</p>	<p>N=16,608 5.6 years (mean duration of follow-up) Extension phase:</p>	<p>Primary: Endometrial cancer incidence Secondary: Not reported</p>	<p>Primary: Over cumulative follow-up, continuous combined estrogen plus progestin use decreased endometrial cancer incidence (66 case patients, 0.06% per year) compared with placebo (95 case patients, 0.10% per year; HR, 0.65; 95% CI, 0.48 to 0.89; P=0.007). While there were somewhat fewer endometrial cancers during intervention (25 vs 30, respectively; HR, 0.77; 95% CI, 0.45 to 1.31), the difference became statistically significant postintervention (41 vs 65, respectively; HR, 0.59; 95% CI, 0.40 to 0.88; P=0.008), but hazard ratios did not differ between phases (P_{difference}=0.46).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>single pill: Prempro® vs placebo</p>		<p>N=12,788 13.2 years (mean duration of follow-up)</p>		<p>There was a statistically nonsignificant reduction in deaths from endometrial cancer in the estrogen plus progestin group (5 vs 11 deaths, HR, 0.42; 95% CI, 0.15 to 1.22). Secondary: Not reported</p>
<p>LaCroix et al.⁵⁷ (2011) CEE 0.0625 mg once daily vs placebo</p>	<p>DB, MC, PC, RCT Postmenopausal women 50 to 79 years of age with prior hysterectomy</p>	<p>N=7,645 10.7 years (mean duration of follow-up)</p>	<p>Primary: CHD, invasive breast cancer Secondary: Stroke, PE, colorectal cancer, hip fracture, death</p>	<p>Primary: The post-intervention risk (annualized risk) for CHD among patients receiving CEE was 0.64% compared to 0.67% with patients receiving placebo (HR, 0.97; 95% CI, 0.75 to 1.25) and 0.26 vs 0.34%, respectively, for breast cancer (HR, 0.75; 95% CI, 0.51 to 1.09). Over the entire follow-up, lower breast cancer incidence with CEE persisted and was 0.27% compared to 0.35% with placebo (HR, 0.77; 95% CI, 0.62 to 0.92). Health outcomes were more favorable for younger compared to older women for CHD (P=0.05). Secondary: The risk of stroke was no longer evaluated during the post-intervention follow-up period and was 0.36 and 0.41% among patients receiving CEE and placebo (HR, 0.89; 95% CI, 0.64 to 1.24). The risk of deep vein thrombosis was 0.17 and 0.27%, respectively, among patients receiving CEE and patients receiving placebo (HR, 0.63; 95% CI, 0.41 to 0.98) and the risk of hip fracture did not differ significantly between the two treatments (0.36 vs 0.28%; HR, 1.27; 95% CI, 0.88 to 1.28). The post-intervention risk (annualized risk) for total mortality among patients receiving CEE was 1.47% compared to 1.48% with placebo (HR, 1.00; 95% CI, 0.84 to 1.18). Health outcomes were more favorable for younger compared to older patients for total MI (P=0.007), colorectal cancer (P=0.04), total mortality (P=0.04), and global index of chronic disease (P=0.009).</p>
<p>Espeland et al.⁵⁸ (2004)</p>	<p>DB, MC, PC, RCT</p>	<p>N=2,808</p>	<p>Primary: Global cognitive</p>	<p>Primary: The mean 3MSE scores were 0.26 units lower in the estrogen treatment</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>WHIMS</p> <p>CEE 0.625 mg once daily</p> <p>vs</p> <p>placebo</p>	<p>Postmenopausal women, 65 to 79 years of age, with prior hysterectomy</p>	<p>5.4 years (mean follow-up duration)</p>	<p>function as measured by 3MSE</p> <p>Secondary: Not reported</p>	<p>group compared to placebo group (P=0.04).</p> <p>In the group of women with lower cognitive function at baseline, there were significant decreases in 3MSE scores in the estrogen group compared with placebo (P<0.01).</p> <p>The RR of having a 10-unit decrease in 3MSE scores, or greater than 2 standard deviations below the mean, was estimated to be 1.47 (95% CI, 1.04 to 2.07).</p> <p>Secondary: Not reported</p>
<p>Chen et al.⁵⁹ (2006)</p> <p>Nurses' Health Study</p> <p>Conjugated estrogens, with various doses but mostly 0.625 mg once daily</p> <p>vs</p> <p>placebo</p>	<p>PRO</p> <p>Postmenopausal women who had a hysterectomy</p>	<p>N=28,835</p> <p>20 years (mean duration not specified)</p>	<p>Primary: Diagnosis of invasive breast cancer</p> <p>Secondary: Not reported</p>	<p>Primary: The risk of invasive breast cancer was significantly elevated with longer durations of use (P<0.001). The RRs for invasive breast cancer with unopposed estrogen use is 0.96 (95% CI, 0.75 to 1.22) with less than 5 years of use, 0.90 (95% CI, 0.73 to 1.12) with 5 to 9.9 years of use, 1.06 (95% CI, 0.87 to 1.30) with 10 to 14.9 years of use, 1.18 (95% CI, 0.95 to 1.48) with 15.0 to 19.9 years of use, and 1.42 (95% CI, 1.13 to 1.77) with ≥20 years of use.</p> <p>The risk of estrogen receptor and progesterone receptor positive breast cancer was significantly higher after 15 or more years of unopposed estrogen use (P<0.001).</p> <p>Secondary: Not reported</p>
<p>Jackson et al.⁶⁰ (2006)</p> <p>CEE 0.625 mg daily</p> <p>vs</p> <p>placebo</p>	<p>RCT</p> <p>Postmenopausal women 50 to 79 years of age with hysterectomy</p>	<p>N=10,739</p> <p>7.1 years</p>	<p>Primary: Hip fractures and all other fractures</p> <p>Secondary: Not reported</p>	<p>Primary: CEE reduced the risk of hip (HR, 0.65; 95% CI, 0.45 to 0.94), clinical vertebral (HR, 0.64; 95% CI, 0.44 to 0.93), wrist/lower arm (HR, 0.58; 95% CI, 0.47 to 0.72), and total fracture (HR, 0.71; 95% CI, 0.64 to 0.80). This reduction did not differ among strata according to age, oophorectomy status, past hormone use, race/ethnicity, fall frequency, physical activity, or fracture history.</p> <p>Total fracture reduction was lower in women at the lowest predicted fracture risk in both absolute and relative terms (HR, 0.86; 95% CI, 0.68 to</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>1.08). The HRs of the global index for CEE were relatively balanced. The summary of fracture is as follows: lowest risk: HR, 0.81; 95% CI, 0.62 to 1.05; midrisk: HR, 1.09; 95% CI, 0.92 to 1.30; highest risk: HR, 1.04; 95% CI, 0.88 to 1.23 (P=0.42).</p> <p>Secondary: Not reported</p>
<p>Schaefer et al.⁶¹ (2009)</p> <p>Transdermal 17β-estradiol 0.014 mg/day (Menostar[®])</p> <p>vs</p> <p>raloxifene 60 mg/day</p>	<p>AC, DB, MC, RCT</p> <p>Osteopenic postmenopausal women</p>	<p>N=500</p> <p>2 years</p>	<p>Primary: Percent change from baseline in bone mineral density at the lumbar spine</p> <p>Secondary: Proportion of women with no loss of bone mineral density in lumbar spine, change in bone mineral density at hip, biochemical markers of bone turnover, and safety parameters.</p>	<p>Primary: Lumbar spine bone mineral density increased by 2.4% (95% CI, 1.9 to 2.9) with transdermal 17β-estradiol versus 3.0% (95% CI, 2.5 to 3.5) with raloxifene after two years.</p> <p>Secondary: Of those patients taking transdermal 17β-estradiol, 77.3% had no bone loss in the lumbar spine compared to 80.5% of those taking raloxifene.</p> <p>Both treatments were well tolerated. Most women (99% in the transdermal 17β-estradiol group and 100% in the raloxifene group) showed no histological evidence of endometrial stimulation after two years. Mean dense area in breast mammograms was 19.8% in the transdermal 17β-estradiol group vs 19.0% in the raloxifene group after two years.</p>
<p>Haines et al.⁶² (2009)</p> <p>Transdermal estradiol patch (0.014 mg/day)</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Symptomatic postmenopausal Asian women 40 to 65 years of age, had undergone natural menopause, and had \geq24 hot flashes</p>	<p>N=165</p> <p>12 weeks</p>	<p>Primary: Relative change in the frequency of all hot flashes from baseline to week 12</p> <p>Secondary: Relative changes in frequency of all hot flashes from</p>	<p>Primary: There was a greater relative reduction in the mean weekly number of all hot flashes at week 12 with estradiol transdermal patch (55%) compared to placebo (40%; P<0.01), as well as at weeks four and eight.</p> <p>Secondary: The relative change in the number of moderate and severe hot flashes per week at week 12 was greater with estradiol transdermal patch compared to placebo (-58 vs -39%). The reductions of moderate and severe hot flashes and in any hot flashes were significant (P<0.05) at weeks four, eight, and 12.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>baseline to weeks four and eight and frequency of moderate to severe hot flushes from baseline to weeks four, eight, and 12; absolute changes in vaginal pH; vaginal maturation value; Menopause QOL scores; occurrence of urogenital symptoms; vaginal bleeding profiles; safety</p>	<p>Vaginal pH had fallen significantly with estradiol transdermal patch by week four (5.60 ± 0.76 to 5.10 ± 0.72) and then remained stable throughout the trial. There were no significant changes with placebo. Vaginal pH decreased significantly more with estradiol transdermal patch compared to placebo ($P < 0.001$).</p> <p>The vaginal maturation value had increased significantly more with estradiol transdermal patch compared to placebo (absolute change at week 12: 17.40 ± 21.85 vs 5.00 ± 17.04; $P < 0.001$).</p> <p>Of the patients with an intact uterus (53 and 46), few had vaginal bleeding or spotting. Any bleeding/spotting was reported by three patients receiving estradiol transdermal patch and four patients receiving placebo in cycle 1, by two and two in cycle 2, by five and two in cycle 3.</p> <p>The absolute mean change in the Menopause QOL scores from baseline to week 12 were not difference between the treatments (-1.00 ± 1.25 and -1.00 ± 1.06, respectively; P value not reported). All subscores improved with both treatments; vasomotor and sexual subscores improved more with estradiol transdermal patch compared to placebo, while the physical subscore improved more with placebo.</p> <p>There was considerable improvement from baseline in certain urogenital symptoms with both treatments; however, there were no differences between the two treatments for any symptoms assessed.</p> <p>Of the 55 patients who experienced an adverse event, 41.3 and 27.5% received estradiol transdermal patch and placebo. Most events were mild to moderate. The most frequent primary system organ classes with adverse events were the same with both treatments: infections and infestations reproductive system and breast disorders.</p>
<p>Buster et al.⁶³ (2008) Transdermal estradiol spray</p>	<p>DB, MC, PG, RCT Postmenopausal women with at least eight moderate-to-</p>	<p>N=454 12 weeks</p>	<p>Primary: Mean change from baseline in frequency and severity of</p>	<p>Primary: All three dosing regimen groups (one, two or three sprays daily) of the estradiol group showed a significant decrease in hot flushes at weeks four and 12 compared with their placebo groups ($P < 0.010$). The mean change in frequency at week 12 was eight fewer flushes per day for women in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	severe hot flushes per day		moderate-to-severe hot flushes at weeks four and 12 Secondary: Safety	estrogen groups and between four and six fewer flushes for women in the placebo groups. Women in the three- and two-estrogen spray groups demonstrated significant ($P<0.050$) reductions in severity score at weeks four and 12; women in the one-spray group showed significant reductions at week five. At week 12, the majority (74 to 85%) of women on estrogen showed at least a 50% hot flush frequency reduction as compared with 46% in the placebo group. The systemic estrogen delivery rates at week 12 were approximately 0.021, 0.029, and 0.040 mg/d for the one-, two-, and three-spray doses, respectively. Secondary: Common adverse events were similar to those previously reported with other transdermal products. Treatment-related application site reaction rate was similar to placebo (1.3 compared to 1.8%).
Hodis et al. ⁶⁴ (2016) ELITE Oral 17 β -estradiol (1 mg per day, plus progesterone [45 mg] vaginal gel administered sequentially [i.e., once daily for 10 days of each 30-day cycle] for women with a uterus) vs placebo (plus sequential placebo vaginal gel for	DB, PC, RCT Healthy postmenopausal women, stratified according to time since menopause (<6 years [early postmenopause] or ≥ 10 years [late postmenopause])	N=643 Median of 5 years	Primary: Rate of change in carotid-artery intima-media thickness (CIMT) Secondary: Coronary atherosclerosis by cardiac computed tomography (CT)	Primary: After a median 5-year intervention, the effect of hormone therapy on CIMT progression differed between the early and late postmenopause strata ($P=0.007$ for the interaction). In the early-postmenopause stratum, the rate of CIMT progression was significantly lower in the estradiol group than in the placebo group; the absolute difference between the estradiol and placebo groups in the mean progression rate was -0.0034 mm per year (95% CI, -0.0062 to -0.0008 ; $P=0.008$). In the late-postmenopause stratum, the rates of CIMT progression were similar in the estradiol and placebo groups (difference, 0.0012 mm per year; 95% CI, -0.0009 to 0.0032; $P=0.29$). The effect of hormone therapy on the absolute value of CIMT at five years also differed significantly between the early and late postmenopause strata ($P=0.03$ for the interaction). Secondary: Although the measures of coronary atherosclerosis were significantly greater among women in the late-postmenopause stratum than among those in the early-postmenopause stratum, the CT measures did not differ significantly between the placebo and estradiol groups within either postmenopause stratum.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
women with a uterus)				
Comparative Trials of Estrogens With Same Delivery Route				
<p>Mizunuma et al.⁶⁵ (2010)</p> <p>Estradiol 0.5 mg/day</p> <p>vs</p> <p>estradiol 1 mg/day</p> <p>vs</p> <p>placebo</p> <p>Patients originally randomized to placebo were switched to estradiol 1 mg/day after 52 weeks for ethical reasons.</p> <p>Patients with an intact uterus, received estradiol/levonorgestrel 0.5 mg/40 µg or 1 mg/40 µg daily.</p> <p>All patients received daily calcium and vitamin D supplementation.</p>	<p>DB, MC, PC, RCT</p> <p>Japanese women 45 to 75 years of age who had experienced natural menopause or undergone bilateral oophorectomy ≥1 year prior to trial enrollment with osteoporosis; patients with an intact uterus had a diagnostically valid negative endometrial biopsy or, for those from whom no tissue was obtained or tissue was insufficient for diagnosis, an endometrial thickness ≤4 mm on transvaginal ultrasound</p>	<p>N=309</p> <p>2 years</p>	<p>Primary: Percentage change in lumbar BMD at 52 weeks, serial percentage change in lumbar BMD during 104 weeks</p> <p>Secondary: Change in amenorrhea rate; incidence of endometrial hyperplasia at 52 and 104 weeks; percentage change in bone turnover markers; changes in calcium, inorganic phosphate, and creatinine levels; fractures</p>	<p>Primary: A total of 241 patients completed all assessments. Combined data of patients receiving monotherapy and combination therapy revealed that the percentage change in lumbar BMD at 52 weeks was significantly greater with estradiol 1 (P<0.001) and 0.5 mg (P<0.001) compared to placebo. The increase in BMD was nonsignificantly greater with estradiol 1 mg compared to estradiol 0.5 mg (P value not reported). Lumbar BMD did not change with placebo.</p> <p>Mean percentage changes in lumbar BMD continued to increase for 104 weeks, reaching 8.0 and 10.2% at 104 weeks with estradiol 0.5 and 1 mg, respectively. At this point, the difference between estradiol 0.5 and 1 mg was significant (P=0.008). There was a greater percentage change in BMD with estradiol 1 mg compared to estradiol 0.5 mg, both overall and in patients receiving combination therapy. In repeated measurement analysis, neither the estradiol dose nor the presence or absence of levonorgestrel had a significant effect (P=0.058 and P=0.192, respectively).</p> <p>The osteoporosis cure rate (percentage of patients with BMD >-2.5 SD of young adult mean) was greater with estradiol 1 mg (44, 50, and 60% of patients at 28, 52, and 104 weeks, respectively) compared to estradiol 0.5 mg (35, 44, and 50%, respectively).</p> <p>Secondary: The amenorrhea rate was greater with estradiol/levonorgestrel 0.5 mg/40 µg compared to estradiol/levonorgestrel 1 mg/40 µg at both 52 and 104 weeks.</p> <p>Levonorgestrel effectively suppressed possible endometrial proliferation due to estradiol administration. Neither endometrial hyperplasia nor cancer was observed at 52 and 104 weeks among patients who received estradiol/levonorgestrel 1 mg/40 µg. There was no clear difference in the incidence rates of atrophic/inactive endometrium between placebo and combination therapy. Endometrial thickness increased slightly over time</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>with combination therapy without clinical significance.</p> <p>Intact osteocalcin, bone alkaline phosphatase, type 1 collagen cross-linked N-telopeptide, and deoxypyridinoline all decreased with estradiol treatment to within the reference range, and changes were consistent with the change in BMD. Bone resorption markers decreased first, followed by bone formation markers. Urine type 1 collagen cross-linked N-telopeptide, urine deoxypyridinoline, and serum bone alkaline phosphatase achieved the minimum significant change. Changes in bone formation markers were greater with estradiol 1 mg compared to estradiol 0.5 mg at 52 and 104 weeks, but this was not significant. There was no difference between active treatments in changes in bone resorption markers. There was no excessive suppression of bone turnover markers with active treatment.</p> <p>Six patients experienced new fractures in the 104 weeks; four patients receiving placebo, one patient receiving estradiol 0.5 mg, and one patient receiving estradiol 1 mg. Levonorgestrel had no effect on the fracture rate.</p>
<p>Good et al.⁶⁶ (1996)</p> <p>Transdermal estradiol patch (Alora[®]) 50 µg/day</p> <p>vs</p> <p>transdermal estradiol patch (Alora[®]) 100 µg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, PG, RCT</p> <p>Postmenopausal women ≥21 years of age if surgically menopausal or ≥45 years of age if naturally menopausal, amenorrheic for ≥6 months, experiencing ≥60 moderate or severe hot flashes weekly</p>	<p>N=273</p> <p>12 weeks</p>	<p>Primary: Reduction in the frequency and severity of hot flashes</p> <p>Secondary: Changes in serum concentrations of estradiol, estrone, estrone sulfate, and FSH; improvements in vaginal cytology; global impressions; adverse events</p>	<p>Primary: There was a significant reduction in the frequency of moderate-to-severe hot flashes by week three of treatment with the 50 µg/day dose (P<0.02) and by week two of treatment with the 100 µg/day dose (P<0.001) compared with placebo.</p> <p>At the end of the study, there was a reduction in frequency of moderate-to-severe hot flashes by 86.6% with the 50 µg/day dose and by 92.5% with the 100 µg/day dose.</p> <p>Forty eight percent of the 50 µg/day group and 68% of the 100 µg/day group did not experience any hot flashes by week 12.</p> <p>Secondary: The changes in estradiol, estrone, and estrone sulfate were increased in a dose-dependent manner.</p> <p>Serum FSH levels were reduced in a dose-dependent manner.</p> <p>Both treatment groups showed improvement in vaginal cytology.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Both treatment groups reported improvement in vaginal dryness, itching and dyspareunia. Greater improvement was reported with the 100 µg/day group.</p> <p>The median assessment scores showed patients and investigators rated active treatment as good or excellent and placebo treatment as fair.</p> <p>The number of systemic adverse experiences was similar (71.4% of patients on active treatment and 73.6% of patients on placebo).</p>
<p>Bowen et al.⁶⁷ (1998)</p> <p>Transdermal estradiol patch (Alora®) 0.1 mg/day</p> <p>vs</p> <p>transdermal estradiol patch (Estraderm®) 0.1 mg/day</p>	<p>OL, RCT, XO</p> <p>Postmenopausal women between 35 to 65 years of age</p>	<p>N=24</p> <p>30 days (11 days of treatment with first drug, then 7 days of washout interval, then crossover to second drug for 11 days of treatment)</p>	<p>Primary: Serum estradiol concentrations; FI defined as $[C_{\max} - C_{\min}]/C_{\text{av}}$</p> <p>Secondary: Monitoring metabolism of estradiol to estrone and estrone sulphate, local skin tolerability defined as application site reactions such as erythema and pruritus</p>	<p>Primary: Peak estradiol levels were similar (127.1 for Alora® vs 128.6 for Estraderm®; P=0.5228). However, Alora® had fewer fluctuations in steady-state levels. Alora® had an FI of 0.970 ± 0.226, while Estraderm® had an FI of 1.684 ± 0.452 (P=0.0001).</p> <p>Secondary: The peak estrone levels (47.7 vs 36.4) and estrone sulphate levels (1,383.7 vs 1,085.9) were higher with Alora® than Estraderm®.</p> <p>There were fewer fluctuations in steady-state levels of estrone (FI of 0.955 ± 0.338 vs 1.351 ± 0.467) and estrone sulphate (FI of 1.031 ± 0.386 vs 1.483 ± 0.366) with Alora® than Estraderm®.</p> <p>The incidences of erythema (45.8 vs 25%) and pruritus (45.8 vs 29%) were higher in the Estraderm® group than in the Alora® group.</p> <p>There were no severe adverse events reported for either treatment.</p>
<p>Ibarra de Palacios et al.⁶⁸ (2002)</p> <p>Transdermal estradiol patch (Estradot®*) 50 µg/day</p>	<p>OL, RCT</p> <p>Healthy postmenopausal women</p>	<p>N=100</p> <p>7 days</p>	<p>Primary: Skin irritation and adhesion, estradiol delivery</p> <p>Secondary: Not reported</p>	<p>Primary: The Estradot® group had lower erythema scores and lower incidences of very slight erythema (P=0.0028) than the Climara® group.</p> <p>There was more adherence and fewer incidences of detachment with the Estradot® than with Climara® (not statistically significant).</p> <p>Both transdermal patches had similar delivery of estradiol.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs transdermal estradiol patch (Climara®) 50 µg/day				Secondary: Not reported
Archer et al. ⁶⁹ (1994) CEE 0.625 mg once daily plus MPA 2.5 mg (Group A) or 5 mg (Group B) once daily vs CEE 0.625 mg once daily plus MPA 5 mg (Group C) or 10 mg (Group D) once daily on the last 14 days of each 28 day cycle vs placebo once daily (Group E)	DB, MC, RCT Postmenopausal women	N=1,724 1 year	Primary: Bleeding patterns Secondary: Not reported	Primary: Amenorrhea occurred in 40% of the patients in Group A, 50% of the patients in Group B, 5% of the patients in Group C or D, and 50% of the patients in Group E. Regular withdrawal bleeding or spotting occurred in 81.3% of Group C and 77.0% of Group D. There was no bleeding or spotting in 75.5% of Group E. Secondary: Not reported
Archer et al. ⁷⁰ (1999) Transdermal estradiol 50 µg/day (Vivelle®)	DB, MC, RCT Postmenopausal women, 40 to 70 years of age, with an intact uterus	N=625 1 year	Primary: Incidences of endometrial hyperplasia, bleeding and/or spotting,	Primary: There were significantly fewer cases of endometrial hyperplasia in the estradiol/norethindrone acetate group than in the estradiol group (P<0.001). There was a longer mean duration of irregular bleeding or spotting in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>transdermal estradiol 50 µg plus norethindrone acetate 140, 250, or 400 µg/day (Combipatch®)</p>			<p>vasomotor events</p> <p>Secondary: Not reported</p>	<p>estradiol group compared to the estradiol/norethindrone acetate group.</p> <p>There was a higher incidence of no uterine bleeding in the estradiol/norethindrone acetate group than in the estradiol group.</p> <p>Similar reductions in mean number of hot flashes and intensity of sweating were observed with all treatment groups.</p> <p>Secondary: Not reported</p>
<p>Harrison et al.⁷¹ (2002)</p> <p>Transdermal estradiol patch (generic) 0.1 mg/24 hours once weekly, applied to buttocks</p> <p>vs</p> <p>transdermal estradiol patch (Climara®) 0.1 mg/24 hours once weekly, applied to buttocks</p>	<p>OL, RCT, XO</p> <p>Postmenopausal women, 45 to 70 years of age</p>	<p>N=42</p> <p>7 days</p>	<p>Primary: Estradiol, estrone, and estrone sulfate levels, application site irritation, patch adhesion</p> <p>Secondary: Not reported</p>	<p>Primary: The C_{max} levels for the two treatments were outside the interval of 0.80 and 1.25, suggesting non-bioequivalence when the patches are applied to the buttocks.</p> <p>Treatment with the generic estradiol patch vs Climara® resulted in more application site reactions (19.5 vs 2.4%) and skin irritations (three incidences of moderate erythema with generic patch vs 1 incidence of intense erythema with Climara®; P=0.039). Both patches resulted in a score of 0 or no visible reaction by day 5 of treatment.</p> <p>Higher incidences of detachment (3 vs 1) and patch lifting (22 vs 6) were reported with the generic patch vs Climara®. Thus, the OR for detachment or lifting of the patch was 6.95 (P<0.001) for the generic estradiol patch compared to Climara®.</p> <p>Secondary: Not reported</p>
<p>Pornel et al.⁷² (1995)</p> <p>Transdermal estradiol patch (Menorest®) 50 µg/24 hours twice weekly</p>	<p>MC, OL, PG, RCT</p> <p>Postmenopausal women with moderate-to-severe vasomotor symptoms, 39 to 64 years of age</p>	<p>N=205</p> <p>12 weeks</p>	<p>Primary: Mean number of hot flashes per day, severity of menopausal symptoms, erythema and pruritus at application sites</p>	<p>Primary: Both treatments resulted in significant improvement in number of hot flashes per day at week 12 (P=0.005). There was no statistically significant difference in mean number of hot flashes between treatment groups at week 12.</p> <p>Both treatments showed improvement in the severity of sweats, sleep disturbances, urogenital symptoms, and depression.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs transdermal estradiol patch (Estraderm®) 50 µg /24 hours twice weekly			Secondary: Not reported	There were less topical adverse events, such as erythema and pruritus, in the Menorest® group compared with the Estraderm® group, which did not reach statistical significance (P=0.15). Secondary: Not reported
Toole et al. ⁷³ (2002) Transdermal estradiol patch (Estradot®*) 50 µg/24 hours vs transdermal estradiol patch (Menorest®†) 50 µg/24 hours	OL, RCT Healthy postmenopausal women, 40 to 70 years of age	N=208 5 weeks	Primary: Skin irritation as measured by erythema Secondary: Skin reaction, patch adherence, adhesive residue and sensitization	Primary: There was significantly less skin irritation with Estradot® than Menorest® (P=0.0001). Secondary: There were more skin reactions with Menorest® than Estradot® (2.40 vs 0.48%). There was a higher number of patches that detached in the Menorest® group compared to Estradot® group (P=0.0253). There was a significantly higher percentage of patients with residue in the Menorest® than Estradot® group (10.10 vs 1.92%; P<0.0001). There were no differences between groups in sensitization.
Erianne et al. ⁷⁴ (1997) Menorest®† matrix (without drug) twice weekly vs Estraderm® matrix (without drug) twice weekly	MC, OL Normal healthy females over 40 years of age	N=275 21 days	Primary: Skin irritation, pruritus (by direct questioning), and adhesion Secondary: Not reported	Primary: There were fewer incidences of skin irritation with Estraderm® compared with Menorest® (11.9 vs 15.9% on the buttocks and 13.7 vs 18.6% on the abdomen). There were fewer incidences of pruritus with Estraderm® compared with Menorest® (92.5 vs 95.9% on the buttocks and 88.7 vs 96.3% on the abdomen). There were similar percentages of patches that were fully adhered to the buttocks application sites during treatment for both groups. There were more patches fully adhered to the abdomen application sites with the Menorest® group compared to the Estraderm® group (88.7 vs 75.8%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Andersson et al.⁷⁵ (2000)</p> <p>Transdermal estradiol patch (Menorest®) 50 µg/24 hours twice weekly</p> <p>vs</p> <p>transdermal estradiol (Climara®) 50 µg/24 hours once weekly</p>	<p>OL, RCT, XO</p> <p>Healthy postmenopausal women</p>	<p>N=20</p> <p>8 weeks</p>	<p>Primary: Bioavailability, pharmacokinetics, tolerability</p> <p>Secondary: Not reported</p>	<p>Not reported</p> <p>Primary: There were no differences between the groups in AUC, C_{max}, C_{min}, average concentrations, or fluctuations.</p> <p>There were three cases of erythema with Menorest® and 21 cases of skin reactions in 15 subjects treated with Climara®.</p> <p>There were eight systemic adverse events in 8 subjects treated with Menorest® and 13 systemic adverse events in 10 subjects treated with Climara®.</p> <p>Secondary: Not reported</p>
<p>Suckling et al.⁷⁶ (2006)</p> <p>Intravaginal estrogens (creams, tablets, pessaries, and an estradiol-releasing ring)</p>	<p>MA</p> <p>Postmenopausal women with vaginitis or vaginal atrophy</p>	<p>N=4,162 (19 trials)</p> <p>≥3 months</p>	<p>Primary: Efficacy (improvement in vaginal atrophy measured both objectively and subjectively), safety (assessment of endometrial stimulations, breast pain) and acceptability (measures of withdrawal, adherence, acceptability of treatment to women)</p> <p>Secondary:</p>	<p>Primary: The estradiol ring showed an improvement of pruritus (two RCTs: OR, 2.71; 95% CI, 1.66 to 4.43) when compared to estrogen cream. In the ring versus tablets trials, there were significant improvements in the tablet group for vaginal dryness (two RCTs: OR, 0.40; 95% CI, 0.24 to 0.64), dyspareunia (two RCTs: OR, 0.53; 95% CI, 0.36 to 0.78), and frequency (two RCTs: OR, 0.63; 95% CI, 0.41 to 0.95). Compared to the cream group, the tablet group showed an improvement for vaginal dryness (one RCT: OR, 7.00; 95% CI, 1.64 to 29.85).</p> <p>The estradiol ring versus placebo ring showed an improvement for freedom of symptoms of dyspareunia (one RCT: OR, 12.67; 95% CI, 3.23 to 49.67). The estrogen tablets versus placebo showed an improvement for burning and itching symptoms (two RCTs: OR, 0.15; 95% CI, 0.10 to 0.20) and dyspareunia (two RCTs: OR, 0.17; 95% CI, 0.12 to 0.23). An improvement in vaginal dryness was seen in the vaginal tablet group when compared to placebo (three RCTs: OR, 0.08; 95% CI, 0.06 to 0.10).</p> <p>There were no significant differences between groups (estradiol ring versus estrogen cream, estradiol ring versus estrogen tablets, estradiol tablets</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	<p>versus placebo) for the following outcomes: dysuria, nocturia, urgency, urge incontinence, participant symptom improvement in dryness, urge incontinence, soreness and irritation, loss of sexual desire and vaginitis.</p> <p>Significant findings for the relief of vaginal atrophy favored the cream, ring, and tablets when compared to placebo.</p> <p>One trial showed significant adverse effects (including uterine bleeding, breast pain and perineal pain) of CEE cream compared to estradiol tablets (OR, 0.18; 95% CI, 0.07 to 0.50). Two trials showed endometrial overstimulation with CEE cream compared to the ring (OR, 0.29; 95% CI, 0.11 to 0.78).</p> <p>Secondary: Not reported</p>
Comparative Trials of Estrogens With Different Delivery Routes				
<p>Yang et al.⁷⁷ (2007)</p> <p>Oestrogen[®] gel (1.25 g daily; 2.5 g daily; 5.0 g daily)</p> <p>vs</p> <p>control (Estrinol [Ovestin[®]] 2 mg/day)</p> <p>All women received calcium carbonate, 500 mg/day of elemental calcium.</p>	<p>PRO</p> <p>Postmenopausal women</p>	<p>N=82</p> <p>1 year</p>	<p>Primary: BMD evaluated by 1 QCT at baseline (before treatment), then at six-month intervals</p> <p>Secondary: Not reported</p>	<p>Primary: At 12-month posttreatment of Oestrogen[®] versus estrinol 2 mg/day, Oestrogen[®] showed the following BMD changes at the respected doses: 1.25 g/day showed BMD change of 4.82%; P=0.017; 2.5 g/day BMD change of 2.72%; P=0.226; and 5.0 g/day BMD change of 8.69%; P=0.051).</p> <p>At 6 months, all Oestrogen[®] groups showed significant increases in lumbar spine BMD after treatment (P<0.05), except for the Oestrogen[®] gel 1.25 g/day group (P=0.232).</p> <p>Secondary: Not reported</p>
<p>Polvani et al.⁷⁸ (1991)</p>	<p>MC, RCT</p> <p>Postmenopausal</p>	<p>N=460</p> <p>6 months</p>	<p>Primary: Menopausal symptoms,</p>	<p>Primary: There were similar improvements in menopausal symptoms and similar effects on the endometrium with both treatments.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Oral CEE, dose not specified</p> <p>vs</p> <p>transdermal estradiol, dose not specified</p>	<p>women</p>		<p>bleeding</p> <p>Secondary: Not reported</p>	<p>The quality and duration of bleeding were considered more physiological in the transdermal group than in the oral group.</p> <p>The transdermal estradiol group showed better compliance and fewer dropouts.</p> <p>Secondary: Not reported</p>
<p>Cortellaro et al.⁷⁹ (1991)</p> <p>Transdermal estradiol 0.05 mg/day</p> <p>vs</p> <p>CEE 0.625 mg orally once daily</p> <p>Both groups in combination with MPA 10 mg once daily on the last 8 days of each cycle</p>	<p>OL, RCT</p> <p>Postmenopausal women</p>	<p>N=45</p> <p>4 months</p>	<p>Primary: Menopausal symptoms, lipid profile, serum estradiol levels</p> <p>Secondary: Not reported</p>	<p>Primary: Both treatments provided similar relief in postmenopausal symptoms.</p> <p>Both treatments resulted in similar reductions in serum TC and LDL-C. There was a significant decrease in serum TG levels with the transdermal estradiol treatment only.</p> <p>There were no differences between treatment groups in plasma calcium and phosphorus levels or clotting factors.</p> <p>Only transdermal estradiol resulted in early follicular-phase plasma estradiol levels.</p> <p>Secondary: Not reported</p>
<p>Pattison et al.⁸⁰ (1989)</p> <p>Transdermal estradiol patch 50 µg/24 hours</p> <p>vs</p> <p>ethinyl estradiol 20 µg orally once</p>	<p>DB, XO</p> <p>Postmenopausal women</p>	<p>N=25</p> <p>Duration not specified</p>	<p>Primary: Menopausal symptoms, vaginal cytology, gonadotropin levels, urinary calcium levels, menstrual pattern, hepatic proteins</p> <p>Secondary:</p>	<p>Primary: Both treatments improved menopausal symptoms and vaginal cytology.</p> <p>Both treatments lowered gonadotrophin levels and urinary calcium loss.</p> <p>Transdermal estradiol did not have an effect on hepatic function, while oral ethinyl estradiol had adverse effects on hepatic proteins (sex-hormone-binding globulin, plasma renin substrate, and lipoproteins).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily			Not reported	
Hirvonen et al. ⁸¹ (1987) Estradiol plus MPA, dose not specified vs estradiol plus levonorgestrel, dose not specified vs estradiol valerate 2 mg daily	DB, XO Postmenopausal women	N=36 Duration not specified	Primary: Menopausal symptoms, lipid profile, bleeding episodes Secondary: Not reported	Primary: There were no differences in relief of menopausal symptoms between treatment groups. Women on the estradiol/MPA treatment significantly improved the atherogenic index, which is the LDL-C:HDL-C. Women on the estradiol/levonorgestrel treatment showed deterioration in the atherogenic index. There was more withdrawal bleeding in the estrogen plus progestin group than in the unopposed estrogen group (78 vs 22%). Secondary: Not reported
Place et al. ⁸² (1985) Oral CEE (Premarin [®]) 0.625 mg or 1.25 mg once daily vs transdermal 17 β -estradiol (Estraderm [®]) 0.1 mg/day	DB, MC, PG, RCT Postmenopausal women whose symptoms were satisfactorily controlled with CEE	N=124 Duration not specified	Primary: Menopausal symptoms, adverse effects Secondary: Not reported	Primary: There were no significant differences between the treatment groups in hot flashes, other postmenopausal symptoms such as sweating, insomnia, headache, vaginal symptoms, urinary urgency, global assessment scores or estrogen-related side effects. There were minor topical reactions reported with the transdermal estradiol for about 20% of the study period. Secondary: Not reported
Al-Azzawi et al. ⁸³ (2003) Estradiol acetate vaginal ring	DB, MC, PG, PRO, RCT Healthy postmenopausal	N=159 24 weeks	Primary: Hot flashes, night sweats, urogenital symptoms, adverse events	Primary: Both treatments resulted in significant improvement in hot flashes and night sweats at 12 and 24 weeks from baseline. Reduction in urogenital symptoms was seen with both treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(Menoring[®]‡) that releases 50 µg/day of estradiol plus placebo oral tablet once daily</p> <p>vs</p> <p>oral estradiol 1 mg once daily plus placebo vaginal ring</p>	<p>women, <65 years, with moderate-to-severe vasomotor symptoms (defined as ≥20 hot flashes/night sweats per week)</p>		<p>Secondary: Not reported</p>	<p>Both groups reported similar incidences of adverse events, including local effects.</p> <p>Secondary: Not reported</p>
<p>Nachtigall.⁸⁴ (1995)</p> <p>Estradiol vaginal ring that releases 7.5 µg/24 hours of estradiol</p> <p>vs</p> <p>conjugated estrogen vaginal cream, 2 g three times a week</p>	<p>MC, OL, PG, RCT</p> <p>Postmenopausal women with estrogen-deficiency-derived atrophic vaginitis</p>	<p>N=196</p> <p>15 weeks</p>	<p>Primary: Urogenital atrophy/symptoms, physicians' and patients' assessment of symptoms</p> <p>Secondary: Frequency of endometrial over stimulation as determined by progestogen challenge test after treatment period</p>	<p>Primary: The vaginal ring and creams produced similar improvements in vaginal dryness, vaginal burning, dyspareunia, and vaginal pH.</p> <p>Physicians' and patients' assessment of both treatments were similar.</p> <p>Secondary: More patients treated with the cream demonstrated signs of endometrial proliferation or hyperplasia than with the ring (10 vs 5%).</p> <p>There were more episodes of bleeding with the progestogen challenge test in the vaginal cream group than the vaginal ring group.</p>
<p>Hilditch et al.⁸⁵ (1996)</p> <p>Oral CEE (Premarin[®]) 0.625 mg once daily</p> <p>vs</p>	<p>DB, RCT</p> <p>Women 2 to 7 years after menopause, with intact uterus and ovaries, not currently on hormone therapy,</p>	<p>N=74</p> <p>112 days (four 28-day cycles)</p>	<p>Primary: QOL, determined using the Menopause-Specific QOL Questionnaire</p> <p>Secondary:</p>	<p>Primary: There were significant improvements in QOL scores, but no differences between treatment groups were observed in scores for vasomotor, physical, psychosocial, or sexual domains (P>0.05).</p> <p>There was a significant improvement from baseline to 10 weeks in scores for vasomotor and physical domains (P<0.001), while changes from 10 weeks to 14 weeks were not statistically significant.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>transdermal estradiol-17β (Estraderm[®]) 50 μg twice weekly</p> <p>Both groups in combination with oral MPA (Provera[®]) 10 mg once daily for the last 12 days of each cycle</p>	<p>and on average severely symptomatic</p>		<p>Not reported</p>	<p>There was significant improvement from baseline to six weeks in scores for psychosocial and sexual domains (P<0.01), while changes from six weeks to the end of study were not statistically significant.</p> <p>Secondary: Not reported</p>
<p>Blanc et al.⁸⁶ (1998)</p> <p>Percutaneous 17β-estradiol gel 1.5 mg/day (Group A)</p> <p>vs</p> <p>transdermal 17β-estradiol patch 50 μg/day (Group B)</p> <p>vs</p> <p>oral estradiol valerate 2 mg once daily (Group C)</p> <p>All groups in combination with a progestin, noregestrol acetate 2.5 mg</p>	<p>MC, OL, PRO, RCT</p> <p>Postmenopausal women, mean, 54.9\pm0.6 years of age</p>	<p>N=54</p> <p>168 days (six 28-day cycles)</p>	<p>Primary: Rate of amenorrhea</p> <p>Secondary: Climacteric symptoms</p>	<p>Primary: The amenorrhea rates after one month of treatment were 67 to 83% for Group A, 25 to 56% for Group B, and 53 to 61% for Group C, which were significantly different between groups for the fourth (P=0.008) and fifth (P=0.003) treatment cycles.</p> <p>The overall rate of cycles with no bleeding was 78% for Group A, 48% for Group B, and 60% for Group C (P=0.001).</p> <p>Secondary: There were no significant differences between groups in relief of climacteric symptoms by the end of the third cycle.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily				
Polatti et al. ⁸⁷ (2000) Oral estradiol valerate 2 mg once daily for 21 days plus cyproterone acetate 1 mg once daily for 21 days of each 28-day cycle vs transdermal estradiol 50 µg for 21 days plus MPA 10 mg orally once daily for 10 days of each 28-day cycle	PRO, RCT Postmenopausal women with and without uterine myomas	N=240 2 years	Primary: Risk of uterine myoma onset or progression Secondary: Not reported	Primary: Among the patients without uterine myomas at baseline, 5% of the transdermal estradiol/MPA group developed new onset of myomas while no new cases of uterine myomas were reported in the oral estradiol valerate/cyproterone acetate group (P<0.01). Among the patients with uterine myomas at baseline, treatment with transdermal estradiol/MPA resulted in a mean increase in myoma volumes of 25.3% compared with initial volume of myoma (P<0.01). On the contrary, treatment with oral estradiol valerate/cyproterone acetate resulted in no significant changes in myoma volumes. Secondary: Not reported
Jarvinen et al. ⁸⁸ (2001) Transdermal estradiol patch (Evorel®) 50 µg/24 hours vs transdermal estradiol gel (Divigel®) 1.0 mg	OL, RCT, XO Healthy postmenopausal women	N=24 18 days	Primary: Estradiol levels Secondary: Not reported	Primary: There were no significant differences in peak estradiol levels (C _{max}) or area under the time-concentration curve (AUC) between groups. Estradiol levels fluctuated more with the patch. The total coefficient of variability for AUC was 39% for the patch versus 35% for the gel. Secondary: Not reported
Nelson et al. ⁸⁹ (2004)	MA	N=32 trials	Primary: Efficacy as	Primary: The numbers of hot flashes per week were significantly reduced with all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Oral CEE</p> <p>vs</p> <p>oral 17β-estradiol</p> <p>vs</p> <p>transdermal 17β-estradiol</p>	<p>Postmenopausal women with hot flashes</p>	<p>Duration varied</p>	<p>measured by relief of hot flashes, adverse effects</p> <p>Secondary: Not reported</p>	<p>forms of estrogen compared with placebo. Treatment with oral CEE resulted in a mean change in the number of hot flashes per week of -19.1 (95% CI, -33.0 to -5.1). Treatment with oral 17β-estradiol group resulted in a mean change of -16.8 (95% CI, -23.4 to -10.2). Treatment with transdermal 17β-estradiol group resulted in a mean change of -22.4 (95% CI, -35.9 to -10.4). There was no significant difference between the agents in treatment of menopausal hot flashes.</p> <p>The estrogen agents showed similar short-term adverse effects. Breast tenderness and atypical vaginal bleeding were the most frequently reported adverse effects.</p> <p>Secondary: Not reported</p>
<p>Studd et al.⁹⁰ (1995)</p> <p>Transdermal estradiol patch (Menorest[®]†) 50 μg/24 hours twice weekly plus dydrogesterone 20 mg for 12 days of every 28-day cycle</p> <p>vs</p> <p>CEE (Premarin[®]) 0.625 mg orally once daily plus dydrogesterone 20 mg for 12 days of every 28-day cycle</p>	<p>DB, DD, MC, PG, RCT</p> <p>Postmenopausal women 40 to 65 years of age, with moderate-to-severe vasomotor symptoms (defined as \geq21 hot flashes per week)</p>	<p>N=214</p> <p>12 weeks</p>	<p>Primary: Number of hot flashes per day</p> <p>Secondary: Other menopausal symptoms, severity of hot flashes, global assessment, and hormone levels</p>	<p>Primary: The number of daily hot flashes decreased significantly in both treatment groups compared with baseline (7.14 to 0.92 in the Menorest[®] group and 6.66 to 0.54 in the Premarin[®] group). No statistically significant difference was observed between the two treatment groups at 12 weeks (P=0.36).</p> <p>Secondary: Menopausal symptoms significantly improved in both treatment groups, with 98% of the patients reporting no severe vasomotor symptoms at 12 weeks. There was no statistically significant difference in menopausal symptoms improvements between the groups.</p> <p>There was no statistically significant difference in global assessment scores between groups as reported by the investigator (P=0.63) or the patient (P=0.71).</p> <p>There was no significant difference between the groups in mean plasma estradiol (P=0.37) or estrone (P=0.56) levels at posttreatment. The mean estradiol to estrone ratio was similar in both groups (0.72 for Menorest[®] and 0.70 for Premarin[®]).</p> <p>The number of severe adverse events was similar in both groups (7% for Menorest[®] and 9% for Premarin[®]).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Good et al.⁹¹ (1999)</p> <p>Transdermal estradiol patch (Alora[®]) 0.05 mg/day administered twice weekly</p> <p>vs</p> <p>transdermal estradiol patch (Alora[®]) 0.1 mg/day administered twice weekly</p> <p>vs</p> <p>CEE 0.625 mg once daily</p> <p>vs</p> <p>CEE 1.25 mg once daily</p>	<p>DB, DD, PG, RCT</p> <p>Highly symptomatic postmenopausal women</p>	<p>N=321</p> <p>12 weeks</p>	<p>Primary: Frequency and severity of hot flashes</p> <p>Secondary: Not reported</p>	<p>Primary: There were no significant differences in the frequency of hot flashes or the frequency of moderate-to-severe hot flashes between the Alora[®] 0.05 mg/day and CEE 0.625 mg groups or Alora[®] 0.1 mg/day and CEE 1.25 mg groups at week 12.</p> <p>There were no significant differences in vaginal cytology, breast tenderness, and unexpected vaginal bleeding between the transdermal and oral estrogen groups. However, there was a lower incidence of bleeding in the Alora[®] 0.05 mg/day group.</p> <p>Secondary: Not reported</p>
<p>Chetkowski et al.⁹² (1986)</p> <p>Transdermal estradiol 25, 50, 100, or 200 µg per 24 hours</p> <p>vs</p>	<p>Dose-response study</p> <p>Postmenopausal women</p>	<p>N=23</p> <p>Duration not specified</p>	<p>Primary: Levels of estradiol and estrone, renin substrate, SHBG, TBG, CBG, lipoproteins</p> <p>Secondary: Not reported</p>	<p>Primary: Transdermal estradiol increased levels of circulating estradiol and estrone, while oral estrogens increased levels of estrone.</p> <p>There were significant increases in circulating levels of renin substrate, SHBG, TBG, and CBG with the oral estrogens, but there was no effect with transdermal estradiol.</p> <p>The oral estrogens at higher doses showed significant improvement in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oral conjugated estrogens 0.625 or 1.25 mg once daily				concentrations of LDL-C and HDL-C, while transdermal estradiol did not. Secondary: Not reported
Manonai et al. ⁹³ (2001) Estradiol vaginal tablet 25 µg vs conjugated estrogen cream 1 g	RCT Postmenopausal women	N=53 12 weeks	Primary: Urogenital symptoms, vaginal health index, vaginal cytology, endometrial thickness, estradiol level Secondary: Not reported	Primary: There was improvement from baseline to four weeks of treatment with both groups in urogenital symptoms, vaginal health index, and vaginal cytology. There were significant improvements in vaginal dryness and dyspareunia with the conjugated estrogen cream compared to vaginal tablet. Secondary: Not reported
Slater et al. ⁹⁴ (2001) Oral micronized estradiol 1 mg daily for 16 months vs transdermal estradiol patch 0.05 mg/day or 0.1 mg/day, changed twice weekly for 9 months vs placebo for 9 months	RETRO Healthy postmenopausal women	N=33 9 to 16 months	Primary: Serum estrone sulfate levels Secondary: Not reported	Primary: There were higher levels of serum estrone sulfate after long-term treatment with oral estradiol than transdermal estradiol. The serum estrone sulfate levels were 38.8 ng/mL at 15 months for oral estradiol, 1.8 ng/mL at nine months for transdermal estradiol 0.05 mg/day, and 3.2 ng/mL at nine months for transdermal estradiol 0.1 mg/day. The increase in serum estrone sulfate level was only significant in the oral estradiol group when compared to baseline (P<0.01). Secondary: Not reported
Pornel ⁹⁵	DB, PG, RCT	N=214	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(1996)</p> <p>Transdermal estradiol patch (Menorest®) 50 µg/24 hours</p> <p>vs</p> <p>CEE (Premarin®) 0.625 mg/day (Study 1) or transdermal estradiol patch (Estraderm®) 50 µg/24 hours (Study 2)</p>	<p>(Study 1); OL, PG (Study 2)</p> <p>Postmenopausal women</p>	<p>(Study 1)</p> <p>N=205 (Study 2)</p> <p>Duration not specified</p>	<p>Hot flashes and other menopausal symptoms, serum estradiol, lipid profile, adverse events</p> <p>Secondary: Not reported</p>	<p>There were improvements in menopausal symptoms with all treatment groups.</p> <p>There were no significant differences in serum estradiol levels or systemic adverse events between treatment groups.</p> <p>There were small reductions in cholesterol in both studies.</p> <p>Menorest® was better tolerated and had a lower incidence of erythema, and pruritus.</p> <p>Secondary: Not reported</p>
<p>Ayton et al.⁹⁶ (1996)</p> <p>Estradiol vaginal ring (Estring®)</p> <p>vs</p> <p>CEE vaginal cream (Premarin®), 1 g (0.625 mg of CEE)</p>	<p>MC, OL, PG, RCT</p> <p>Postmenopausal women with symptoms and signs of urogenital atrophy</p>	<p>N=194</p> <p>12 weeks</p>	<p>Primary: Urogenital symptoms</p> <p>Secondary: Patient preference</p>	<p>Primary: No significant difference was noted between treatment groups in improvement of vaginal dryness and dyspareunia, resolution of atrophic signs, vaginal mucosal maturation indices, and vaginal pH.</p> <p>No significant difference was noted between treatment groups in incidences of intercurrent bleeding episodes.</p> <p>Secondary: The vaginal ring was significantly preferred and accepted by more patients than the vaginal cream (P<0.0001).</p>
<p>Studd et al.⁹⁷ (1996)</p> <p>Transdermal estradiol patch (Menorest®) 50 µg/24 hours twice weekly</p>	<p>RCT</p> <p>Postmenopausal women</p>	<p>N=32</p> <p>1 year</p>	<p>Primary: Menopausal symptoms, bone loss prevention as measured by bone mineral density</p> <p>Secondary: Not reported</p>	<p>Primary: Both treatments resulted in similar relief of menopausal symptoms (vasomotor, psychological, and urogenital symptoms) and reduction of hot flashes.</p> <p>Both treatments resulted in similar lumbar spine and hip densitometry results.</p> <p>Both treatments resulted in similar incidences of adverse events.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>CEE (Premarin®) 0.625 mg orally once daily</p> <p>Both groups in combination with dydrogesterone 20 mg orally for the last 12 days of each 28 day cycle</p>				<p>Secondary: Not reported</p>
<p>Gordon et al.⁹⁸ (1995)</p> <p>Study 1: Estradiol patch 0.05 or 0.1 mg/day changed once weekly</p> <p>vs</p> <p>placebo</p> <p>Study 2: Estradiol patch 0.05 or 0.1 mg/day changed once weekly</p> <p>vs</p> <p>CEE 0.625 mg orally once daily</p>	<p>RCT</p> <p>Healthy postmenopausal women with hot flashes</p>	<p>N=24</p> <p>18 days</p>	<p>Primary: Frequency and severity of hot flashes, subjects' and investigators' global assessment of treatment</p> <p>Secondary: Not reported</p>	<p>Primary: There were significant improvements from baseline in frequency and severity of hot flashes and higher global assessment scores with all treatments in both studies.</p> <p>In Study 2, there was more improvement that did not reach statistical significance in hot flashes with the estradiol patch 0.1 mg/day than with CEE and less improvement with estradiol patch 0.05 mg/day than with CEE.</p> <p>The patches were generally well tolerated.</p> <p>Secondary: Not reported</p>
<p>Shifren et al.⁹⁹ (2008)</p>	<p>OL, XO</p>	<p>N=27</p>	<p>Primary: CRP, IL-6, E- and</p>	<p>Primary: Nine parameters changed significantly during oral CEE: CRP (192%;</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>CEE 0.625 mg/day plus micronized progesterone 100 mg/day for 12 weeks</p> <p>vs</p> <p>transdermal estradiol 0.05 mg/day plus micronized progesterone 100 mg/day for 12 weeks</p>	<p>Naturally menopausal women</p>	<p>24 weeks</p>	<p>P-selectin, ICAM-1 and vascular cell adhesion molecule-1, serum amyloid A, transferrin, prealbumin, IGF-I, SHBG, TBG, CBG</p> <p>Secondary: Not reported</p>	<p>P<0.001); E-selectin (-16.3%; P=0.003); P-selectin (-15.3%; P=0.012); ICAM-1 (-5%; P=0.015); transferrin (5.3%; P=0.024); IGF-I (-30.5%; P<0.001); SHBG (113%; P<0.001); TBG (38%; P<0.001); and CBG (20%; P<0.001).</p> <p>With transdermal estradiol, only three parameters changed significantly and to a lesser degree: ICAM-1 (-2.1%; P=0.04); IGF-I (-12.5%; P<0.001); and SHBG (2.6%; P=0.042).</p> <p>During oral CEE the intrasubject changes in CRP correlated strongly with the changes in serum amyloid A ($r=0.805$; $P<0.001$), and were only weakly associated with the changes in SHBG ($r=0.248$; non-significant), TBG (0.430; $P=0.031$), and CBG ($r=0.072$; non-significant).</p> <p>The log-log relationship between CRP and IL-6 observed at baseline showed a parallel shift during oral CEE, suggesting an amplified hepatic response or a greater sensitivity to IL-6 stimulation.</p> <p>Secondary: Not reported</p>
<p>Vrablik et al.¹⁰⁰ (2008)</p> <p>Oral 17β-estradiol for 12 weeks</p> <p>vs</p> <p>transdermal 17β-estradiol for 12 weeks</p>	<p>OL, XO</p> <p>Hysterectomized women</p>	<p>N=41</p> <p>24 weeks</p>	<p>Primary: Plasma lipid and lipoprotein levels, AIP</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>Oral estrogen replacement therapy resulted in a significant increase in HDL-C and apolipoprotein A-I levels, whereas it significantly decreased TC and LDL-C and increased TG concentrations. Transdermal estrogen replacement therapy had no such effect.</p> <p>Oral estrogen replacement therapy led to a significant TG enrichment of HDL-C (0.19 ± 0.06 vs 0.27 ± 0.07 mmol/L, $P<0.001$) and LDL particles (0.23 ± 0.08 vs 0.26 ± 0.10 mmol/L, $P<0.001$) compared with baseline, whereas transdermal therapy did not have any effect on lipoprotein subclasses composition.</p> <p>The difference between the two treatments was statistically significant for HDL-C:TG and LDL-C:TG (0.27 ± 0.07 vs 0.19 ± 0.05 mmol/L, $P<0.001$ and 0.26 ± 0.10 vs 0.22 ± 0.07 mmol/L, $P<0.001$, respectively).</p> <p>The transdermal but not oral estrogen replacement therapy significantly</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>reduced the AIP compared with baseline (-0.17±0.26 vs -0.23±0.25; P=0.023), making the difference between the therapies statistically significant (-0.23±0.25 vs -0.18±0.22; P=0.017).</p> <p>Oral administration of estrogen replacement therapy resulted in TG enrichment of LDL and HDL particles. Transdermal estrogen replacement therapy did not change the composition of the lipoproteins and produced a significant improvement of AIP. Compared with transdermal estrogen replacement therapy, orally administered estrogen replacement therapy changes negatively the composition of plasma lipoproteins.</p> <p>Secondary: Not reported</p>
<p>Gupta et al.¹⁰¹ (2008)</p> <p>Transdermal estradiol patch</p> <p>vs</p> <p>vaginal estradiol ring</p>	<p>RCT</p> <p>Postmenopausal women</p>	<p>N=24</p> <p>12 weeks</p>	<p>Primary: Serum estradiol, estrone, estrone sulfate, FSH, luteinizing hormone, and SHBG were measured by immunoassay at baseline and six and 12 weeks</p> <p>Secondary: Not reported</p>	<p>Primary: The estradiol patch significantly increased serum estrone and estradiol levels at six and 12 weeks (P<0.01); there was no significant increase in serum estrone and estradiol levels with the estradiol ring.</p> <p>Both the patch and the ring significantly reduced vaginal pH at six (P<0.001) and 12 (P<0.001) weeks and significantly reduced the percentage of vaginal parabasal cells at 12 weeks with no significant difference between the two groups.</p> <p>Both preparations increased the proportion of superficial cells; the increase was significant only with the estradiol patch (P=0.04).</p> <p>Secondary: Not reported</p>
<p>Lethaby et al.¹⁰² (2016)</p> <p>Intravaginal estrogen preparations (ring, tablets, cream)</p>	<p>MA (30 RCTs)</p> <p>Postmenopausal women</p>	<p>N=6,235</p> <p>≥12 weeks</p>	<p>Primary: Efficacy (improvement in symptoms) and safety (endometrial thickness)</p> <p>Secondary: Improvement in</p>	<p>Primary: There was no evidence of a difference in the proportions of women who reported improvement in symptoms of vaginal atrophy between the following treatment comparisons: estrogen ring and estrogen cream, estrogen ring and estrogen tablets, estrogen tablets and estrogen cream, estrogen cream and isoflavone gel. However, a higher proportion of women reported improvement in symptoms in the following active treatments compared with placebo: estrogen ring vs placebo, estrogen tablets vs placebo, and estrogen cream vs placebo. In the case of estrogen</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>symptoms (clinician-assessed), other adverse events (breast disorders e.g. breast pain, enlargement or engorgement, total adverse events, excluding breast disorders) and adherence to treatment</p>	<p>tablets vs placebo and using a random-effect model for analysis of the data because of substantial heterogeneity, there was no longer evidence of a difference in effect on improvement in symptoms.</p> <p>With respect to safety, a higher proportion of women who received estrogen cream showed evidence of increase in endometrial thickness compared to those who were treated with estrogen ring, which may have been due to the higher doses of cream used. However, there was no evidence of a difference in the proportions of women with increase in thickness of the lining of the womb between estrogen tablets and estrogen cream.</p> <p>Secondary: From the overall body of the findings, there was no conclusive evidence of a difference in efficacy between the various estrogenic preparations compared with each other. For safety, there was no conclusive evidence of a difference in the main adverse events (endometrial thickness, breast disorders and total adverse events) between estrogenic preparations vs each other or placebo.</p>
Trials of Combination Estrogen Products				
<p>Hulley et al.¹⁰³ (1998)</p> <p>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Postmenopausal women with established coronary disease, younger than 80 years of age (mean age was 66.7 years), with an intact uterus</p>	<p>N=2,763</p> <p>4.1 years (average follow-up duration)</p>	<p>Primary: Occurrence of nonfatal MI or CHD death</p> <p>Secondary: Coronary revascularization, unstable angina, CHF, cardiac arrest, stroke or transient ischemic attack, peripheral arterial disease, all-cause mortality, fractures, cancers, thromboembolic</p>	<p>Primary: There were no significant differences between groups in occurrences of MI or CHD death (HR, 0.99; 95% CI, 0.80 to 1.22).</p> <p>There were more CHD events in the hormone-treated group compared with placebo in the first year of treatment and fewer events in years four and five. The HR was 1.52 in year one, 1.00 in year two, 0.87 in year three, and 0.67 in years four and five (P=0.009).</p> <p>Secondary: There were no significant differences between groups in the rates of fractures (P=0.59 to 0.82), cancers (P=0.33 to 0.60), and total mortality (P=0.56).</p> <p>There were more of the following outcomes in the hormone group compared with the placebo group: venous thromboembolic events (P=0.002), deep vein thromboses (P=0.004), pulmonary emboli (P=0.08),</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Hulley et al.¹⁰⁴ (2002) HERS and HERSII</p> <p>CEE 0.625 mg once daily plus MPA 2.5 mg once daily</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT followed by OL, OS</p> <p>Postmenopausal women with coronary disease and average of 67 years of age at enrollment in study</p>	<p>N=2,321</p> <p>4.1 years (HERS) followed by 2.7 years of open-label observational study (HERS II)</p>	<p>events, gallbladder disease</p> <p>Primary: Thromboembolic events, biliary tract surgery, cancer, fracture, total mortality</p> <p>Secondary: Not reported</p>	<p>and gallbladder diseases (P=0.05).</p> <p>Primary: The percentages of patients that reported >80% adherence to hormone therapy were 81, 78, 74, 67, 50, and 45% for years one through six, respectively.</p> <p>Hormone therapy was associated with a significant increase in the incidence of deep vein thrombosis compared with placebo (4.5 events per 1,000 person-years vs 2.2; P=0.02).</p> <p>Hormone therapy was associated with a significant increase in the incidence of PE compared with placebo (2.0 events per 1,000 person-years vs 0.7; P=0.03).</p> <p>The incidence of biliary tract surgery was significantly increased with hormone therapy compared with placebo (19.1 events per 1,000 person-years vs 12.9; P=0.005).</p> <p>The rate of cancer was 19% higher in the hormone therapy group than in the placebo group, but did not reach statistical significance (P=0.08 to 0.48).</p> <p>There were no significant differences in the rates of fractures or death between the groups (P>0.05 for both).</p> <p>Secondary: Not reported</p>
<p>Grady et al.⁴⁹ (2002) HERS and HERSII</p> <p>CEE 0.625 mg plus MPA 2.5 mg once daily</p> <p>vs</p>	<p>DB, MC, PC, RCT</p> <p>Postmenopausal women with CHD, average 67 years of age at enrollment</p>	<p>N=2,763</p> <p>6.8 years (4.1 years for HERS, then 2.7 years of follow-up for HERS II)</p>	<p>Primary: Nonfatal MI and CHD death</p> <p>Secondary: Coronary revascularization, hospitalization for unstable angina or</p>	<p>Primary: There were no significant differences in the rates of CHD events between groups. The HR was 0.99 (95% CI, 0.81 to 1.22) in HERS, 1.00 (95% CI, 0.77 to 1.29) in HERS II, and 0.99 (95% CI, 0.84 to 1.17) overall.</p> <p>There were no significant differences between groups for nonfatal MI (P>0.05).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo for HERS trial, followed by hormone therapy prescribed at personal physicians' discretion for HERS II study</p>			<p>CHF, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease</p>	<p>There were no significant differences between groups for any of the secondary cardiovascular outcomes ($P > 0.05$ for all) with the exception of higher incidence of nonfatal ventricular arrhythmia in the hormone group compared to the placebo group (HR, 3.30; 95% CI, 1.08 to 10.1).</p> <p>There was no trend of lower risk for CHD events with longer duration of hormone therapy ($P = 0.18$) during the follow-up period of HERS II.</p>
<p>Maki et al.¹⁰⁵ (2007)</p> <p>CEE 0.625 mg plus MPA 2.5 mg daily</p> <p>vs</p> <p>placebo daily</p> <p>Treatments were given for 4 months.</p>	<p>DB, MC, PC, RCT</p> <p>Generally healthy, postmenopausal women with an intact uterus</p>	<p>N=158</p> <p>22 months</p>	<p>Primary: Change from baseline of memory, attention, and subjective cognition</p> <p>Secondary: Change from baseline at month four on additional measures of cognitive function, emotional status, sexuality, and sleep</p>	<p>Primary: Except for an increase in sexual thoughts and sexual interest with hormone therapy ($P = 0.10$ and $P = 0.006$, respectively), there were no significant differences on any cognitive or QOL measures.</p> <p>Secondary: Compared to placebo, symptomatic women in the hormone therapy group showed an improvement in vasomotor symptoms ($P = 0.001$). Specific data was not provided; however, when compared to baseline and placebo, hormone therapy was associated with an improvement in both the incidence and severity of vasomotor symptoms.</p>
<p>Manson et al.¹⁰⁶ (2003)</p> <p>WHI</p> <p>CEE 0.625 mg once daily plus MPA 2.5 mg, in one tablet, once daily</p> <p>vs</p>	<p>RCT</p> <p>Postmenopausal women, 50 to 79 years of age at baseline</p>	<p>N=16,608</p> <p>5.2 years (planned duration was 8.5 years)</p>	<p>Primary: CHD (nonfatal MI or death due to CHD)</p> <p>Secondary: Not reported</p>	<p>Primary: Hormone therapy was associated with an increase in the risk of CHD. The risk of CHD was highest after the first year of hormone use, with a HR of 1.81 (95% CI, 1.09 to 3.01).</p> <p>There was a trend toward a decreasing risk of CHD over time with hormone use, which was statistically significant. The HR for CHD was 1.34 (95% CI, 0.821 to 2.18) after 2 years of hormone therapy, 1.27 (95% CI, 0.64 to 2.50) after 3 years, 1.25 (95% CI, 0.74 to 2.12) after 4 years, 1.45 (95% CI, 0.81 to 2.59) after 5 years, and 0.70 (95% CI, 0.42 to 1.14) after 6 years or longer.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Secondary: Not reported
<p>WHI Writing Group⁴⁷ (2002)</p> <p>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Healthy postmenopausal women, 50 to 79 years of age with an intact uterus</p>	<p>N=16,608</p> <p>5.2 years (mean follow-up duration)</p>	<p>Primary: CHD (nonfatal MI and CHD death), invasive breast cancer</p> <p>Secondary: Stroke, PE, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes</p>	<p>Primary: The estimated HR for CHD was 1.29 (95% CI, 1.02 to 1.63) and breast cancer was 1.26 (95% CI, 1.00 to 1.59).</p> <p>Thus, there were absolute excess risk of an additional seven CHD events and eight invasive breast cancers per 10,000 person-years of treatment with CEE plus MPA.</p> <p>Secondary: The estimated HR for stroke was 1.41 (95% CI, 1.07 to 1.85), PE was 2.13 (95% CI, 1.39 to 3.25), colorectal cancer was 0.63 (95% CI, 0.43 to 0.92), endometrial cancer was 0.83 (95% CI, 0.47 to 1.47), hip fracture was 0.66 (95% CI, 0.45 to 0.98), and death due to other causes was 0.92 (95% CI, 0.74 to 1.14).</p> <p>Thus, there were absolute excess risks of an additional eight strokes and eight PEs per 10,000 person-years of treatment with CEE plus MPA. There were absolute risk reductions of six fewer colorectal cancers and five fewer hip fractures per 10,000 person-years of treatment with hormone therapy.</p>
<p>Reeves et al.¹⁰⁷ (2006)</p> <p>Estrogen (dose not specified)</p> <p>vs</p> <p>estrogen plus progesterone (dose not specified)</p> <p>vs</p> <p>tibolone</p>	<p>ES, OS</p> <p>Postmenopausal women registered with incident breast</p>	<p>N=14,102 registered with incident breast cancer</p> <p>2.7 years (mean time for all women from date of last contact to end of follow-up)</p>	<p>Primary: Incidence of breast cancer and risk of breast cancer</p> <p>Secondary: Not reported</p>	<p>Primary: 14,102 breast cancers were diagnosed and 11,869 (86%) were invasive.</p> <p>The RRs of invasive breast cancer in current users compared with never users of hormone therapy varied according to tumor histology overall (P<0.0001), for users of estrogen-only therapy (P=0.0001), and for users of estrogen-progesterone therapy (P<0.0001).</p> <p>R Rs for both estrogen-only and estrogen- progesterone therapy were greatest for invasive lobular, mixed ductal-lobular and lobular cancer. These risks were generally higher in current users of combined hormone therapy compared with estrogen-only therapy.</p> <p>At estimated duration of use of <5 years, five to nine years, and >10 years, estrogen-only therapy was associated with a lower RR of invasive ductal,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs non estrogen therapy				lobular, and tubular breast cancer when compared to estrogen plus progesterone therapy. Secondary: Not reported
Rossouw et al. ¹⁰⁸ (2007) CEE 0.625 mg/day or placebo (women post hysterectomy) OR CEE 0.625 mg/day plus MPA 2.5 mg/day or placebo (women without hysterectomy)	DB, MC, PC, RCT Healthy postmenopausal women, 50 to -79 years of age based on hysterectomy status	N=27,347 5.2 years (mean follow-up duration)	Primary: CHD (nonfatal MI, CHD death, or silent MI) and stroke, mortality and a global index for trial monitoring Secondary: Not reported	Primary: In women with less than 10 years since the start of menopause, the HR for CHD was 0.76 (95% CI, 0.50 to 1.16); with 10 to 19 years, 1.10 (95% CI, 0.84 to 1.45); and 20 or more years, 1.28 (95% CI, 1.03 to 1.58) (P=0.02). In women of 50 to 59 years of age, the HR for CHD was 0.93 (95% CI, 0.65 to 1.33). Hormone therapy increased the risk of stroke (HR, 1.32; 95% CI, 1.12 to 1.56), but risk did not vary significantly by age or time since menopause. The effects of hormone therapy on total mortality favored younger women (HR of 0.70 for 50 to 59 years; 1.05 for 60 to 69 years, and 1.14 for 70 to 79 years; P=0.06). Secondary: Not reported
Saltpeper et al. ¹⁰⁹ (2006) CEE, oral esterified estrogens or transdermal estrogen, alone or in combination with a progestin vs placebo, calcium supplementation, or no treatment	MA Postmenopausal women	N=33,315 (107 trials) 1.5 years (mean trial duration; range 0.15 to 5 years)	Primary: Net treatment effects for each analysis were pooled using random effects model, subgroup analysis evaluated the effects of transdermal and oral treatment and treatment in diabetic and nondiabetic women Secondary:	Primary: Subgroup analyses showed that oral agents produced greater reductions in LDL-C:HDL-C (-17.4%; 95% CI, -20.0 to -14.9) than transdermal agents (-8.4%; 95% CI, -13.8 to -2.8; P=0.004). Conjugated estrogens produced greater reductions (-22.4%; 95% CI, -25.6 to -19.1) than oral esterified estrogens (-11.3%; 95% CI, -13.2 to -9.4; P<0.0001). Unopposed estrogens and combined hormone therapy produced similar results. Only conjugated estrogens reduced BP (-2.2%; 95% CI, -4.1 to -0.3). Transdermal agents (-0.8%; 95% CI, -3.3 to -1.6) and oral esterified estrogens (-1.3%; 95% CI, -3.1 to -0.5) were not significant. In women without diabetes, hormone therapy reduced abdominal fat (-6.8%; 95% CI, -11.8 to -1.9), HOMA-IR (-12.9%; 95% CI, -17.1 to -8.6) and new-onset diabetes (RR, 0.7; 95% CI, 0.6 to 0.9). Subgroup analyses showed no significant difference in calculated insulin resistance (HOMA-IR) between transdermal agents and oral agents, conjugated and esterified

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	<p>estrogens, or unopposed and combined treatment.</p> <p>In women with diabetes, hormone therapy reduced fasting glucose (-11.5%; 95% CI, -18.0 to -5.1), HOMA-IR (-35.8%; 95% CI, -51.7 to -19.8), LDL-C:HDL-C (-15.7%; 95% CI, -18.0 to -13.5), lipoprotein(a) (-25.0%; 95% CI, -32.9 to -17.1), mean BP (-1.7%; 95% CI, -2.9 to -0.5), E-selectin (-17.3%; 95% CI, -22.4 to -12.1), fibrinogen (-5.5%; 95% CI, -7.8 to -3.2) and plasminogen activator inhibitor-1 (-25.1%; 95% CI, -33.6 to -15.5).</p> <p>Secondary: Not reported</p>
<p>Chlebowski et al.¹¹⁰ (2003) WHI</p> <p>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Postmenopausal women 50 to 79 years of age, with an intact uterus</p>	<p>N=16,608</p> <p>5.2 years (mean follow-up duration)</p>	<p>Primary: Breast cancer number and characteristics, frequency of abnormal mammograms</p> <p>Secondary: Not reported</p>	<p>Primary: There were more cases of total (HR, 1.24; P<0.001) and invasive (HR, 1.24; P=0.003) breast cancer in the hormone-treated group than in the placebo group.</p> <p>Invasive breast cancers in the hormone-treated group compared to placebo group were larger (P=0.04), more likely to be node positive (P=0.03), and diagnosed at a significantly more advanced stage (P=0.04).</p> <p>There was a higher percentage of abnormal mammograms in the hormone-treated group than in the placebo group after the first year in all age groups (P<0.001) and in women 50 to 59 years of age (P<0.001) as well.</p> <p>Secondary: Not reported</p>
<p>Hays et al.¹¹¹ (2003) WHI</p> <p>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily</p> <p>vs</p>	<p>DB, MC, PC, RCT</p> <p>Postmenopausal women 50 to 79 years of age, with an intact uterus</p>	<p>N=16,608 (at baseline and at one year)</p> <p>N=1,511 (for subgroup analysis at three years)</p> <p>3 years</p>	<p>Primary: QOL measures that included functional status, depression score, sleep quality, sexual functioning, cognitive functioning, and menopausal</p>	<p>Primary: There were significant improvement with hormone therapy compared to placebo from baseline to year one in sleep quality (P<0.001), physical functioning (P<0.001), and bodily pain (P<0.001).</p> <p>Among the 574 women 50 to 54 years of age with moderate-to-severe vasomotor symptoms at baseline, hormone therapy at year 1 was associated with significant improvement in sleep (P=0.02) only. All other changes in QOL scores from baseline to year one were nonsignificant (P>0.05 for all).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			symptoms Secondary: Not reported	There were no clinically significant effects on health-related QOL measures at three years of treatment with hormone therapy ($P>0.05$ for all measures). Secondary: Not reported
Shumaker et al. ¹¹² (2003) CEE 0.625 mg plus MPA 2.5 mg vs placebo	RCT Women 65 years of age or older, with an intact uterus, free of probable dementia	N=4,532 5 years	Primary: Incidence of probable dementia Secondary: Incidence of mild cognitive impairment	Primary: The rate of probable dementia in the estrogen plus progestin group was significantly higher than in the placebo group (HR, 2.05; 95% CI, 1.21 to 3.48; 45 vs 22 per 10,000 person-years; $P=0.01$). Secondary: There was no significant difference in the rate of mild cognitive impairment between the treatment and placebo groups (HR, 1.07; 95% CI, 0.74 to 1.55; 63 vs 59; $P=0.72$).
Cravioto et al. ¹¹³ (2011) CEE/MPA 0.625/5.0 mg daily for the first 10 days of every month vs placebo	DB, PC, RCT Women with systemic lupus erythematosus with any 2 of the following criteria: amenorrhea ≥ 6 months, serum FSH ≥ 30 IU/L, menopausal symptoms, and ≥ 48 years of age	N=106 24 months	Primary: Severity of menopausal symptoms Secondary: Treatment discontinuation rates and reasons, safety	Primary: Vasomotor factor decreased significantly over time ($P=0.002$) with differential patterns in relation to treatment ($P=0.027$); with combination hormone therapy, the reduction was more pronounced compared to placebo, at between 1.5 and 2.0 vs between 0.35 and 0.80 points, respectively (scale of 0 to 6). The score reductions with both treatments were observed since the first month of follow-up. Psychological, subjective-somatic, and organic-somatic factors also showed significant reductions along time ($P<0.001$), but their patterns were similar with respect to treatment ($0.123<P<0.727$). With these three factors, baseline scores decreased with both treatments since the first month of follow-up, but a tendency for returning to baseline scores was observed after one year. The sensory-somatic factors did not change significantly over time ($P=0.065$), nor did the pattern differ between treatments ($P=0.968$). During the two year follow-up period, global mean scores for all the factors except for subjective-somatic tended to be smaller with combination HT compared to placebo; however, the effect size of this treatment did not reach significance in any of the five factors. Secondary: Three patients receiving combination hormone therapy and one patient

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>receiving placebo discontinued the trial due to thrombosis. One patient from each treatment group died due to sepsis. However, neither this medical reason nor the other withdrawal causes were significantly different between the two treatments.</p> <p>Few patients reported adverse events during the trial. Headache, nausea, melasma, galactorrhea, and dysmenorrhea were reported with each treatment, intermittently and at low frequency ($\leq 6\%$). Mastalgia was more common with combination hormone therapy compared to placebo at one and six months of treatment (10.20 vs 13.33%; $P < 0.03$).</p>
<p>Van de Weijer et al.¹¹⁴ (2002)</p> <p>17β-estradiol 50, 75, or 100 $\mu\text{g}/24$ hours for 2 weeks followed by 17β-estradiol/levonorgestrel (50/10, 75/15, or 100/20 $\mu\text{g}/24$ hours) for 2 weeks of each month</p>	<p>MC, RCT, XO</p> <p>Postmenopausal women</p>	<p>N=468</p> <p>1 year</p>	<p>Primary: Bleeding patterns</p> <p>Secondary: Not reported</p>	<p>Primary: Higher frequencies of cyclic bleeds, intermittent bleeding, and mean duration of cyclic bleeding were reported with higher dosages of estradiol/levonorgestrel.</p> <p>Recurrence of cyclic bleeds was acceptable for 90% of the subjects.</p> <p>Secondary: Not reported</p>
<p>Sanada et al.¹¹⁵ (2004)</p> <p>CEE 0.625 mg once daily plus MPA 2.5 mg once daily</p> <p>vs</p> <p>transdermal estradiol plus MPA 2.5 mg once</p>	<p>RCT</p> <p>Postmenopausal Japanese women who developed serum TG concentrations >150 mg/dL after taking CEE plus MA for 12 months</p>	<p>N=36</p> <p>3 months</p>	<p>Primary: TG, VLDL-C, LDL-C, HDL-C</p> <p>Secondary: Not reported</p>	<p>Primary: There was a significant decrease in TG and VLDL levels compared with baseline (226.0 ± 43.9 to 110.5 ± 44.1 mg/dL; $P < 0.01$) in the transdermal estradiol group.</p> <p>There were no significant changes in the LDL-C and HDL-C levels in the transdermal estradiol group compared with CEE group.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily				
Cunha et al. ¹¹⁶ (2010) Group 1: Placebo vs Group 2: estradiol/norethindrone 1/0.5 mg/day for 2 months, followed by placebo vs Group 3: estradiol/norethindrone 1/0.5 mg/day for 4 months, followed by placebo	DB, PC, PRO, RCT Postmenopausal women receiving estrogen/progestogen hormone therapy in full doses (CEE/MPA, or progesterone equivalents) for ≥6 months, wanting to discontinue combination hormone therapy due to personal reasons, and combination hormone therapy was prescribed to treat climacteric vasomotor symptoms	N=60 6 months	Primary: Climacteric symptoms evaluated by the Blatt-Kupperman Menopause Index and hot flush score at two, four, and six months Secondary: Not reported	Primary: For both the Blatt-Kupperman Menopause Index and hot flush score, a statistically significant increase in the values were observed at the first evaluation after withdrawing the combination hormone therapy (i.e., after two, four, and six months for Groups 1, 2, and 3), respectively. The hot flush score was statistically different between groups that had already discontinued combination hormone therapy compared to patients who were still receiving treatment at the time of observation; however, there was no significant difference in the first evaluation subsequent to withdrawing combination hormone therapy (two months: Group 1 vs Group 2; P<0.001; Group 1 vs Group 3; P=0.006; and Group 2 vs Group 3; P=0.485; four months: Group 1 vs Group 2; P=1.000; Group 1 vs Group 3; P=0.003; and Group 2 vs Group 3; P=0.010; and six months: Group 1 vs Group 2, Group 1 vs Group 3, and Group 2 vs Group 3; P=1.000 for all). Secondary: Not reported
Simon et al. ¹¹⁷ (2003) Ethinyl estradiol 5 µg plus norethindrone acetate 1 mg, in one tablet, once daily vs placebo	DB, MC, PG, RCT Healthy postmenopausal women with an intact uterus	N=357 1 year	Primary: Incidence and duration of vaginal bleeding Secondary: Not reported	Primary: There were significantly lower incidences of bleeding in the ethinyl estradiol/norethindrone treatment group compared with CEE/MPA group (P<0.05 at all time points). There was no difference in bleeding incidences in the ethinyl estradiol/norethindrone treatment group and placebo group at months four, five, and seven through 12 (P>0.05). The duration of bleeding and/or spotting was significantly shorter in the ethinyl estradiol/norethindrone group than in the CEE/MPA group (P≤0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily (OL arm)				There was a larger percentage of amenorrhea in the ethinyl estradiol/norethindrone group than in the CEE/MPA group (P<0.05). Secondary: Not reported
Simon et al. ¹¹⁸ (2001) Ethinyl estradiol 5 µg once daily vs ethinyl estradiol 5 µg plus norethindrone acetate 0.25 mg once daily vs ethinyl estradiol 5 µg plus norethindrone acetate 1 mg once daily vs ethinyl estradiol 10 µg once daily vs ethinyl estradiol 10	DB, PC, RCT Postmenopausal women	N=945 1 year	Primary: Incidences of bleeding and/or spotting Secondary: Not reported	Primary: There were significantly higher percentages of amenorrhea with ethinyl estradiol/norethindrone acetate treatment than CEE/MPA treatment. At the end of six months, the incidence of amenorrhea was significantly lower with 5 µg ethinyl estradiol plus 1 mg NA (P=0.009) and 10 µg ethinyl estradiol plus 1 mg norethindrone acetate (P=0.006) compared with CEE/MPA. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>µg plus norethindrone acetate 0.5 mg once daily</p> <p>vs</p> <p>ethinyl estradiol 10 µg plus norethindrone acetate 1 mg once daily</p> <p>vs</p> <p>CEE 0.625 mg plus MPA 2.5 mg once daily</p>				
<p>Simon et al.¹¹⁹ (2003)</p> <p>1 mg norethindrone acetate/5 µg ethinyl estradiol (FemHRT[®])</p> <p>vs</p> <p>0.625 mg CEE/2.5 mg or 5 mg MPA (Prempro[®])</p>	<p>RETRO</p> <p>Women who were new users of six hormone therapy regimens</p>	<p>N=7,120</p> <p>9 months</p>	<p>Primary: Treatment continuation rates</p> <p>Secondary: Not reported</p>	<p>Primary: The treatment continuation rate was significantly higher among women taking FemHRT[®] compared to Prempro[®].</p> <p>Significantly higher rates of treatment continuation were observed in women >55 years of age, those who did not switch hormone therapy during the nine months study period, those who received care in the central and northeast regions of the United States, and those who received treatment from obstetricians/gynecologists versus primary care physicians.</p> <p>Secondary: Not reported</p>
<p>Archer et al.¹²⁰ (1999)</p> <p>Transdermal estradiol 50 µg/day</p>	<p>DB, MC, RCT</p> <p>Postmenopausal women, aged 40 to 70, with an intact</p>	<p>N=625</p> <p>1 year</p>	<p>Primary: Incidence of endometrial hyperplasia, bleeding and/or</p>	<p>Primary: There were significantly fewer cases of endometrial hyperplasia in the estradiol/norethindrone acetate treated group than in the estradiol group (P<0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(Vivelle®)</p> <p>vs</p> <p>transdermal estradiol 50 µg plus norethindrone acetate 140, 250, or 400 µg/day (Combipatch®)</p>	<p>uterus</p>		<p>spotting, vasomotor events</p> <p>Secondary: Not reported</p>	<p>There was a longer mean duration of irregular bleeding or spotting in the estradiol group compared to the estradiol/norethindrone acetate.</p> <p>There was a higher incidence of no uterine bleeding in the estradiol/norethindrone acetate group than in the estradiol group.</p> <p>Similar reductions in mean number of hot flashes and intensity of sweating were observed with all treatment groups.</p> <p>Secondary: Not reported</p>
<p>Johnson et al.¹²¹ (2002)</p> <p>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, daily (Prempro®)</p> <p>vs</p> <p>17β-estradiol 1 mg plus norethindrone acetate 0.5 mg, in one tablet, daily (Activella®)</p>	<p>DB, MC, PRO, RCT</p> <p>Healthy postmenopausal women</p>	<p>N=438</p> <p>6 months</p>	<p>Primary: Bleeding profiles</p> <p>Secondary: Lipid profiles</p>	<p>Primary: Treatment with Activella® resulted in a larger percentage of women with no bleeding and no spotting (P=0.001) compared to treatment with Prempro®.</p> <p>Secondary: There was a significant improvement in TG (-8.5 vs 11.7%; P<0.001) and TC (-9.1 vs -6.9%) in the Activella® group compared to Prempro® group.</p>
<p>Godsland et al.¹²² (1993)</p> <p>Oral therapy with CEE 0.625 mg daily plus levonorgestrel 0.075 mg daily for 12 days of each 28 day cycle</p>	<p>PC, RCT</p> <p>Postmenopausal women</p>	<p>N=61</p> <p>18 months</p>	<p>Primary: Intravenous glucose tolerance tests, plasma glucose, insulin, and C-peptide concentrations</p> <p>Secondary: Not reported</p>	<p>Primary: There were no changes in glucose or insulin concentrations with transdermal therapy.</p> <p>Oral hormone therapy lowered glucose tolerance and increased plasma insulin response. There was greater insulin resistance compared with baseline during the combined estrogen/progestin phase than in the estrogen only phase.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>transdermal therapy with continuous 17β-estradiol plus norethindrone acetate 0.25 mg daily for 14 days of each 28-day cycle</p> <p>vs</p> <p>placebo</p>				
<p>Whitcroft et al.¹²³ (1994)</p> <p>Oral therapy with CEE 0.625 mg daily plus dl-norgestrel 0.15 mg daily for 12 days of each cycle</p> <p>vs</p> <p>transdermal therapy with 17β-estradiol 0.05 mg daily plus norethindrone acetate 0.25 mg daily for 14 days of each cycle</p> <p>vs</p>	<p>PC, RCT</p> <p>Healthy postmenopausal women</p>	<p>N=61</p> <p>3 years</p>	<p>Primary: Fasting serum lipid and lipoprotein concentrations</p> <p>Secondary: Not reported</p>	<p>Primary: Both oral and transdermal hormone therapy significantly reduced serum TC (P<0.001) and LDL-C (P<0.01) from three months of treatment and effects were maintained at three years of treatment.</p> <p>Both oral and transdermal hormone therapy significantly reduced serum TG concentrations (P<0.05) from six months of treatment and effects were maintained over three years of treatment only with the transdermal group.</p> <p>HDL-C declined in both oral and transdermal treatment groups, as well as placebo group (P<0.05 for all).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo</p> <p>Hirvonen et al.¹²⁴ (1987)</p> <p>Estradiol plus MPA, dose not specified</p> <p>vs</p> <p>estradiol plus levonorgestrel, dose not specified</p> <p>vs</p> <p>estradiol valerate 2 mg daily</p>	<p>DB, XO</p> <p>Postmenopausal women</p>	<p>N=36</p> <p>Duration not specified</p>	<p>Primary: Menopausal symptoms, lipid profile, bleeding episodes</p> <p>Secondary: Not reported</p>	<p>Primary: There were no differences in relief of menopausal symptoms between treatment groups.</p> <p>Women on the estradiol/MPA treatment significantly improved the atherogenic index, which is the LDL-C:HDL-C. Women on the estradiol/levonorgestrel treatment showed deterioration in the atherogenic index.</p> <p>There was more withdrawal bleeding in the estrogen plus progestin groups than in the unopposed estrogen group (78 vs 22%).</p> <p>Secondary: Not reported</p>
<p>White et al.¹²⁵ (2006)</p> <p>Drospirenone 1, 2, or 3 mg with 17β estradiol 1 mg or once daily in the morning</p> <p>vs</p> <p>17β estradiol 1 mg alone once daily each morning</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Postmenopausal women, 45 to 75 years of age, with mean seated clinic SBP 140 to 179 mm Hg and DBP between 90 to 109 mm Hg in the untreated state</p>	<p>N=750</p> <p>Study duration not specified; placebo phase was 3 to 4 weeks and treatment phase was 8 weeks</p>	<p>Primary: Mean change from baseline at week eight in clinic and in ambulatory SBP</p> <p>Secondary: Changes from baseline in the clinic and 24-hour DBP, assessment of the hourly changes in ambulatory SBP and DBP</p>	<p>Primary: While the mean reduction in clinic BP in the 17β estradiol alone group and 1 mg drospirenone plus 17β estradiol group was not statistically significant, the mean reductions in clinic BP in the 3 and 2 mg drospirenone plus 17β estradiol groups were statistically significant. These reductions were, -13.8/-8.5 and -12.1/-9.2 mm Hg, in the 3 and 2 mg drospirenone plus 17β estradiol groups, respectively, while the reductions for placebo were -8.7/-5.0 mm Hg (SBP reductions; P=0.0004 and 0.0195 for 3 and 2 mg doses; and for DBP reductions; P<0.0001 for both).</p> <p>Secondary: Measures of ambulatory BP showed significant reductions from baseline at a mean of 24-hour SBP in both the 2 and 3 mg drospirenone plus 17β estradiol treatment groups compared to placebo. These reductions were, -6.1 and -4.7 mm Hg in the 3 and 2 mg drospirenone plus 17β estradiol groups respectively, compared to a mean SBP change in the placebo group of -1.2 mm Hg. (P values for SBP reductions vs placebo were <0.0001 and 0.009 respectively). There were no differences in ambulatory BP for 1 mg</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				drospirenone plus 17 β estradiol and 17 β estradiol alone vs placebo.
Preston et al. ¹²⁶ (2005) Drospirenone with 17 β estradiol daily for 28 days vs placebo daily for 28 days	DB, MC, PC, RCT Postmenopausal women, 44 to 70 years of age, with or without type 2 diabetes mellitus and using an angiotensin-converting enzyme or angiotensin II receptor antagonist	N=230 28 days	Primary: Number and percentage subjects who developed hyperkalemia (K \geq 5.5 mEq/L) and changes from baseline in seated clinic BP Secondary: Not reported	Primary: No statistical differences were observed in the overall number and percentage of subjects with hyperkalemia for drospirenone with 17 β estradiol versus placebo. No subject had symptoms or electrocardiographic changes related to hyperkalemia. A reduction in BP was observed at -8.6/-5.8 mm Hg in patients receiving drospirenone with 17 β estradiol vs -3.7/-2.9 mm Hg in the placebo group; P<0.01 for both SBP and DBP. Secondary: Not reported
White et al. ¹²⁷ (2005) Drospirenone 3 mg with 1 mg 17 β estradiol daily in the morning vs placebo daily in the morning	DB, MC, PC, RCT Postmenopausal women, aged 45 to 80 years, with seated clinic SBP of 140 to 159 mm Hg and/or the DBP was 90 to 99 mm Hg	N=213 Duration not specified	Primary: Mean change from baseline at week 12 in clinic BP Secondary: Changes from baseline in the 24-hour systolic and diastolic BPs and heart rate, as well as other ambulatory monitoring parameters and mean changes from baseline of serum potassium	Primary: Mean reductions in clinic BP in the drospirenone with 17 β estradiol group averaged -14.1/-7.9 mm Hg, and the respective reductions for the placebo group were -7.1/-4.3 mm Hg (P<0.001 for both SBP and DBP). Secondary: Drospirenone with 17 β estradiol significantly lowered pulse pressure compared to the placebo group by -3.5 mm Hg (P=0.007). No significant changes were observed in heart rate.
Archer et al. ¹²⁸ (2005) Estradiol 1.0 mg	DB, MC, PG, RCT Postmenopausal	N=1,142 1 year	Primary: Endometrial hyperplasia	Primary: Compared to estradiol alone, the combinations of drospirenone and estradiol were effective in protecting against endometrial hyperplasia. The probability of hyperplasia was 0.060 (95% CI, 0.043 to 0.078) for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>estradiol 1.0 mg plus 0.5, 1.0, 2.0, or 3.0 mg of drospirenone (estradiol plus drospirenone)</p>	<p>women with an intact uterus (42 to 75 years of age)</p>		<p>Secondary: Bleeding patterns, hot flush frequency and severity, urogenital symptoms, and health-related QOL</p>	<p>estradiol monotherapy group, 0.007 for the 2 mg estradiol plus drospirenone group, and nonsignificant for the remaining drospirenone/estradiol groups.</p> <p>Secondary: A greater proportion of women in all estradiol plus drospirenone treatment groups had bleeding in cycles one through three compared to women in the estradiol monotherapy group ($P<0.001$). Beginning at week two, there was a decrease in hot flushes from baseline at all time points ($P\leq 0.008$ in all treatment groups). At cycle 13, a decrease in mean body weight from baseline was observed in the 2 mg estradiol plus drospirenone and 3 mg estradiol plus drospirenone groups ($P<0.001$ for both), while the decrease was not statistically significant in the 0.5 mg estradiol plus drospirenone and 1 mg estradiol plus drospirenone groups.</p>
<p>Schurmann et al.¹²⁹ (2004)</p> <p>Drospirenone 1, 2 or 3 mg combined with estradiol (1 mg)</p> <p>vs</p> <p>placebo</p>	<p>MC, PC, RCT</p> <p>Healthy postmenopausal Caucasian women, 45 to 66 years of age, who complained of at least five moderate-to-severe hot flushes per day on at least 7 of the 14 days preceding the study</p>	<p>N=225</p> <p>16 weeks of treatment; followed with 2 weeks of follow-up</p>	<p>Primary: Change in the frequency and the intensity of hot flushes from baseline</p> <p>Secondary: Other menopausal symptoms (sweating periods, sleep problems, depressed mood, nervousness, and urogenital symptoms), vaginal bleeding, and adverse events</p>	<p>Primary: Hot flushes significantly decreased in frequency for all treatment groups (range, 86 to 90%) in comparison to placebo (45%; $P\leq 0.001$) and remained suppressed at study end, 16 weeks.</p> <p>Secondary: Drospirenone and estradiol treatment decreased the intensity and severity of sweating, sleep problems, depression, nervousness, and urogenital symptoms. The majority of the adverse events were mild or moderate, and similar rates were observed in all groups. Furthermore, no serious adverse events or clinically significant laboratory abnormalities were attributed to the treatment.</p>
<p>Lin et al.¹³⁰ (2011)</p> <p>Estradiol/drospirenone daily</p>	<p>DB, MC, PC, PG, RCT</p> <p>Chinese postmenopausal</p>	<p>N=249</p> <p>16 weeks (2 weeks of follow-up)</p>	<p>Primary: Relative change in number of hot flushes per week, absolute changes in</p>	<p>Primary: The number of hot flushes per week decreased progressively with both treatments over the 16 week period, but was consistently lower with combination therapy compared to placebo from week two onward. Over the treatment period weeks three to 16, the number of hot flushes per week</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	<p>women 45 to 65 years of age with moderate to severe vasomotor symptoms; documentation of ≥ 24 moderate to severe hot flushes over 7 consecutive days during a 3 week screening period; an intact uterus with endometrial thickness < 5 mm, or a normal endometrial biopsy if endometrial thickness > 5 mm; last menstrual bleed ≥ 1 year before, or bilateral oophorectomy ≥ 6 weeks before, or last natural menstrual bleed ≥ 6 months previously, with a serum FSH ≥ 40 mIU/mL; a negative urinary pregnancy test; and a negative bilateral mammography result</p>		<p>the severity of moderate to severe hot flushes and in the severity of all hot flushes from baseline to weeks three to 16</p> <p>Secondary: Changes in other climacteric symptoms from baseline to week 16, safety</p>	<p>was 11.1 ± 15.1 and 22.4 ± 17.3 with combination therapy and placebo, representing absolute decreases of 45.9 ± 29.3 and 27.5 ± 28.1, respectively. These absolute changes corresponded to relative decreases in the number of hot flushes per week of 80.4 and 51.9% with combination therapy and placebo, a significant treatment difference of 28.5% in favor of combination therapy ($P < 0.0001$).</p> <p>Combination therapy was associated with numerically greater reductions in the severity of moderate to severe hot flushes over weeks three to 16 compared to placebo. The change in severity of all hot flushes between baseline and treatment (weeks three to 16) was -0.61 and -0.43 with combination therapy and patients receiving placebo ($P \leq 0.05$).</p> <p>Secondary: Among patients who experienced moderate to severe sweating at baseline, 4.1 (7/169) and 22.2% (12/45) of patients receiving combination therapy and placebo continued to experience moderate to severe sweating at week 16. A significantly higher proportion of patients were free of sweating symptoms after 16 weeks with combination therapy (48.1 vs 73.4%; $P < 0.0001$).</p> <p>Among patients who experienced vaginal dryness at baseline, a significantly greater proportion of patients receiving combination therapy no longer had this symptom compared to placebo (87.7 [93/106] vs 60.0% [21/35]; $P < 0.001$).</p> <p>Depressive moods, nervousness and pollakiuria followed a similar trend of greater reductions in frequency after 16 weeks of combination therapy compared to placebo, but these differences did not reach significance. Incidences of depressive mood were reduced from 42.1% at baseline to 4.0% after combination therapy, and from 49.2 to 12.5% with placebo. Corresponding values for nervousness were from 50 to 51% with both treatments to 6.9 and 17.9% with combination therapy and placebo. At baseline, pollakiuria was present in 29 to 32% of patients and of these, 90.2 and 72.2% no longer experienced this symptom with combination therapy and placebo.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Mild to moderate insomnia was present at baseline in 71.6 and 65.6% of patients randomized to combination therapy and placebo. At week 16, similar proportions of patients (17.9 and 19.6%, respectively) continued to experience insomnia with both treatments. Occurrences of nocturia were similar between the two treatments at baseline (33.3 and 37.7%), and of these patient, 75.9 and 81.0% of patients were free from this symptom at week 16.</p> <p>The proportion of patients free from arthralgia increased from 44.3% at baseline to 75.1% after combination therapy, and from 29.5 to 58.9% with placebo. Proportion of patients free from myalgia increased from 69.9 to 86.1% with combination therapy, and from 57.4 to 78.6% with placebo.</p> <p>Results for the Clinical Global Impressions scale assessment in patients available at week 18 showed a more favorable effect for combination therapy compared to placebo; 87.9 vs 47.3% of patients were 'much improved' or 'very much improved' (P<0.001).</p> <p>A higher proportion of patients receiving combination therapy experienced bleeding and spotting compared to placebo (number of bleeding/spotting days in each 28-day period: 1.7 to 4.8 vs 0.2 to 0.9 days). The cumulative amenorrhea rate in patients who completed the trial increased from 34.4% after cycle one to 67.2% after cycle four with combination therapy, and from 85.2 to 93.4% with placebo.</p> <p>A total of 71 patients (29.1 vs 26.2%) reported at least one adverse event, including 46 patients reporting a possibly treatment-related event (20.8 vs 13.1%). The most common adverse event was breast tenderness (8.7 vs 1.6%). The majority of events were mild to moderate in severity, with severe events including breast tenderness, headache, breast swelling, ankle fracture, increased blood TGs, joint swelling, and abdominal neoplasm. Three serious adverse events were reported and were considered to be nontreatment-related.</p>
Rowan et al. ¹³¹ (2006) Study 1:	Post-hoc analysis of 3 studies Study 1=DB, MC,	N= 220,531 Study 1=16 weeks	Primary: Postmenopausal symptoms, the effects on bone and	Primary: In study 1, norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg was associated with significant reductions from baseline in mean weekly total hot flush frequency from week 4 (63.6%) through week 16 (73.7%);

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Norethindrone acetate/ethinyl estradiol at either 0.2 mg/1 µg, 0.5 mg/2.5 µg, 1 mg/5 µg, or 1 mg/10 µg, or placebo</p> <p>Study 2: norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg, 1 mg/5 µg, or 1 mg/10 µg, or placebo</p> <p>Study 3: Progestin/estrogen therapy (norethindrone acetate/ethinyl estradiol 0.2 mg/1 µg, 0.5 mg/2.5 µg, 1 mg/5 µg, or 1 mg/10 µg), unopposed estrogen monotherapy (ethinyl estradiol 1, 2.5, 5, or 10 µg), or placebo</p>	<p>PC, PG; postmenopausal women</p> <p>Study 2=DB, MC, PG; postmenopausal women</p> <p>Study 3=DB, MC, PC, PG; postmenopausal women</p>	<p>Study 2=12 weeks</p> <p>Study 3=24 months</p>	<p>endometrium</p> <p>Secondary: Not reported</p>	<p>P<0.05).</p> <p>In study 2, the frequency of moderate or severe hot flushes was decreased by 61.1% at week 4 (P<0.05) and by 82.2% at week 12 (P<0.001) with norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg. Furthermore, the mean intensity score was significantly lower than that with placebo at weeks eight and 12 (for both; P=0.001).</p> <p>In study 3, the cumulative amenorrhea rates were approximately 90% in the norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg and placebo groups at 12 months. At 24 months, lumbar spine bone mineral density was maintained with norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg, but was significantly decreased from baseline at 7.4% in the placebo group (P<0.001). At 24 months, endometrial hyperplasia was not observed in the group receiving norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg.</p> <p>Secondary: Not reported</p>
<p>Battaglia et al.¹³² (2009)</p> <p>Estradiol/drospirenone 1 mg/2mg</p>	<p>RCT</p> <p>Postmenopausal women</p>	<p>N=30</p> <p>6 months</p>	<p>Primary: Effects on BP and other surrogate markers of cerebrovascular and cardiovascular</p>	<p>Primary: The basal pulsatility index and the back pressure of the ophthalmic artery were similar in groups 1 and 2. After six months, no changes were observed.</p> <p>The nitrites/nitrates values were not different between groups 1 and 2 both</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>estradiol/ norethisterone acetate 1 mg/0.5mg</p>			<p>risk.</p> <p>Secondary: Not reported</p>	<p>in basal conditions and after therapy.</p> <p>The brachial artery flow-mediated vasodilatation and the pulsatility index of the brachial artery did not show any difference in groups 1 and 2 both in basal conditions and after the therapy.</p> <p>The 24-hour BP monitoring showed no significant differences in the 24-hour time, daytime, and nighttime values either in basal conditions or after therapy.</p> <p>All participants were found to be dippers normally (nocturnal reduction $\geq 10\%$ in comparison with diurnal values). The wake-up BP values were similar in the studied participants.</p> <p>Secondary: Not reported</p>
<p>Furness et al.¹³³ (2009)</p> <p>Estrogen therapy, combined continuous estrogen-progestin therapy, sequential estrogen-progestin therapy</p>	<p>MA</p> <p>Postmenopausal women 40 to 75 years of age</p>	<p>N = 38,702 (45 RCT)</p> <p>>12 months</p>	<p>Primary: Frequency of endometrial hyperplasia (of any type) or adenocarcinoma (assessed by endometrial biopsy)</p> <p>Secondary: Adherence to therapy, rates of additional interventions, and withdrawals due to adverse events</p>	<p>Primary: Unopposed estrogen was associated with increased risk of endometrial hyperplasia at all doses, and durations of therapy between one and three years.</p> <p>For women with a uterus, the risk of endometrial hyperplasia with hormone therapy comprising low dose estrogen continuously combined with a minimum of 1 mg norethisterone acetate or 1.5 mg MPA is not significantly different from placebo (1 mg estradiol/norethindrone acetate: OR, 0.04; 95% CI, 0 to 2.8; 1.5 mg MPA: no hyperplasia events).</p> <p>Secondary: Adherence was greater in both continuous and sequentially combined regimens than in unopposed estrogen regimens. There were significant numbers of participants in most of the trials included who withdrew from the trial prior to completion (10 to 50%) due to adverse events, lack of efficacy, or other reasons. Only one study assessed the rate of unscheduled biopsies and found a significant increase associated with moderate dose unopposed estrogen therapy (1 RCT: OR, 11.8; 95% CI 7.0 to 19.9).</p>
<p>Canonicio et al.¹³⁴ (2008)</p>	<p>MA of 8 OS and 9 RCT</p>	<p>N=not reported</p>	<p>Primary: Risk of VTE</p>	<p>Primary: MA of OS showed that oral estrogen but not transdermal estrogen</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Oral estrogen with or without progestogen</p> <p>vs</p> <p>transdermal estrogen with or without progestogen</p>	<p>Women using hormone replacement therapy (age not reported)</p>	<p>Duration varied</p>	<p>Secondary: Not reported</p>	<p>increased the risk of VTE. Compared to nonusers of estrogen, the OR of first-time VTE in current users of oral estrogen was 2.5 (95% CI, 1.9 to 3.4) and in current users of transdermal estrogen was 1.2 (0.9 to 1.7). Past users of oral estrogen had a similar risk of VTE to never users (P values were not reported).</p> <p>The risk of VTE in women using oral estrogen was higher in the first year of treatment compared to treatment for more than one year (P<0.05).</p> <p>No noticeable difference in the risk of VTE was observed between unopposed oral estrogen and opposed oral estrogen.</p> <p>Results from nine RCTs confirmed the increased risk of VTE among women using oral estrogen (2.1; 95% CI, 1.4 to 3.1; P value not reported).</p> <p>The combination of oral estrogen and thrombogenic mutations or obesity further enhanced the risk of VTE, whereas transdermal estrogen did not seem to confer additional risk in women at high risk of VTE.</p> <p>Secondary: Not reported</p>
<p>Morch et al.¹³⁵ (2009)</p> <p>Oral, transdermal, and vaginal estrogen products with or without a progestogen component</p>	<p>PRO cohort study</p> <p>Danish women 50 to 79 years of age from 1995 through 2005 who had no hormone-related cancers before study entry</p>	<p>N=909,949</p> <p>Average follow-up 8 years</p>	<p>Primary: Incidence of ovarian cancer</p> <p>Secondary: Not reported</p>	<p>Primary: Compared to women who never took hormone therapy, current users of hormones had incidence rate ratios for all ovarian cancers of 1.38 (95% CI, 1.26 to 1.51) and 1.44 (95% CI, 1.30 to 1.58) for epithelial ovarian cancer (P values not reported).</p> <p>The risk declined with years since last use: 0 to 2 years, 1.22; >2 to 4 years, 0.98; >4 to 6 years, 0.72, and >6 year, 0.63.</p> <p>For current users the risk of ovarian cancer did not differ significantly with different hormone therapies or duration of use.</p> <p>The incidence rates in current and never users of hormones were 0.52 and 0.40 per 1,000 years, respectively, for an absolute risk increase of 0.12 (95% CI, 0.01 to 0.17 per 1,000 years; P value not reported). This approximates one extra ovarian cancer for roughly 8,300 women taking</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>hormone therapy each year.</p> <p>Regardless of the duration of use, the formulation, estrogen dose, regimen, progestin type, and route of administration, hormone therapy was associated with an increase risk of ovarian cancer.</p> <p>Secondary: Not reported</p>
<p>Jaakkola et al.¹³⁶ (2012)</p> <p>Estrogen plus progesterone</p> <p>Patient population was compared to background population.</p>	<p>Cohort, PRO</p> <p>Women who had used estrogen/progesterone therapy in 1994 to 2008 for ≥6 months, ≥50 years of age were identified</p>	<p>N=243,857</p> <p>Duration not specified</p>	<p>Primary: Incidence of cervical precancerous or cancerous lesions</p> <p>Secondary Not reported</p>	<p>Primary: Among patients receiving combination hormone therapy, there were 210 patients with squamous lesions (178 precancerous, 32 cancerous) and there were 79 patients with glandular lesions (14 precancerous, 65 adenocarcinomas). The use of combination hormone therapy was not associated with incidence of precancerous lesions, but the risk for squamous cell carcinoma decreased (standardized incidence ratio, 0.41; 95% CI, 0.28 to 0.58) and that for adenocarcinoma increased (1.31; 95% CI, 1.01 to 1.67).</p> <p>After use of combination hormone therapy for five years, the risk for squamous cell carcinoma decreased (standardized incidence ratio, 0.34; 95% CI, 0.16 to 0.65), and the risk for adenocarcinomas increased (1.83; 95% CI, 1.24 to 2.59).</p> <p>Secondary: Not reported</p>
<p>Lobo et al.¹³⁷ (2009)</p> <p>SMART-1</p> <p>Single tablets of BZA (10, 20, or 40 mg), each with CEE (0.625 or 0.45 mg) daily</p> <p>vs</p>	<p>AC, DB, MC, PC, RCT</p> <p>Healthy, postmenopausal women age 40 to 75 with an intact uterus</p>	<p>N=3,397</p> <p>2 years</p>	<p>Primary: Hot flushes, breast pain, vaginal atrophy, metabolic parameters, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: All doses of BZA/CEE provided significantly better relief of hot flushes than placebo at most time points (P<0.01). BZA/CEE groups also demonstrated significant decreases in hot flush number and severity compared to raloxifene.</p> <p>Treatment with BZA (10 mg)/CEE (0.625 or 0.45 mg) and BZA (20 mg)/CEE (0.625 or 0.45 mg) was significantly more effective than placebo in increasing the mean proportion of superficial cells from baseline to most time points (P<0.001).</p> <p>Breast pain occurred with similar frequency for subjects in the BZA/CEE,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>raloxifene 60 mg daily</p> <p>vs</p> <p>placebo taken daily</p>				<p>raloxifene, and placebo groups, and there were no significant differences in the incidence of breast pain among the groups for any 28-day interval.</p> <p>Reductions in LDL cholesterol for all BZA/CEE doses (range, -5.7 to -10.9%) were significantly greater compared to placebo (range, -0.1 to 2.2%) at all time points (P<0.01). Increases in HDL cholesterol for all BZA/CE doses (range, 7.0 to 13.5%) were significantly greater compared to placebo (range, 1.3 to 5.4%) at all time points (P<0.05), and significantly greater compared to raloxifene (range, 3.1 to 6.6%) at most time points (P<0.05).</p> <p>Overall, the incidence of adverse events and serious adverse events was similar among treatment groups. There were no significant differences in the incidence of treatment-emergent adverse events among groups. Overall, the incidence of VTEs was similar for subjects treated with BZA/CEE or placebo (0.76 vs 1.56 per 1,000 women-years, respectively; RR, 0.48; 95% CI, 0.05 to 4.66). The cardiovascular adverse events of interest included myocardial infarction, coronary artery disease, and coronary artery insufficiency. The incidence of cardiovascular adverse events was low (<1%) across all treatment groups, with no significant differences among groups.</p> <p>Secondary: Not reported</p>
<p>Pickar et al.¹³⁸ (2009) SMART-1</p> <p>Single tablets of BZA (10, 20, or 40 mg), each with CEE (0.625 or 0.45 mg) daily</p> <p>vs</p> <p>raloxifene 60 mg</p>	<p>AC, DB, MC, PC, RCT</p> <p>Healthy, postmenopausal women age 40 to 75 with an intact uterus</p>	<p>N=3,397</p> <p>2 years</p>	<p>Primary: Incidence of endometrial hyperplasia at 12 months in the efficacy evaluable population (EEP)</p> <p>Secondary: Adverse events</p>	<p>Primary: At month 12, the incidence of endometrial hyperplasia for all BZA/CEE doses was <1% (predefined acceptable limit was ≤2%), except for BZA (10 mg)/CEE (0.625 mg) (3.81%; CI, 2.27 to 5.99). No hyperplasia was observed with BZA (40 mg)/CEE (0.625 mg), BZA (20 or 40 mg)/CEE (0.45 mg), raloxifene, and placebo. The lowest effective dose of BZA that protected the endometrium from the stimulatory effects of CEE (0.45 and 0.625 mg) was 20 mg, as indicated by acceptable rates of endometrial hyperplasia after one year (primary endpoint) and two years of exposure.</p> <p>Secondary: The incidence of treatment-emergent adverse effects was not significantly different among treatment groups (P=0.696).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs placebo taken daily				
Archer et al. ¹³⁹ (2009) SMART-1 Single tablets of BZA (10, 20, or 40 mg), each with CEE (0.625 or 0.45 mg) daily vs raloxifene 60 mg daily vs placebo taken daily	AC, DB, MC, PC, RCT Healthy, postmenopausal women age 40 to 75 with an intact uterus	N=3,397 2 years	Primary: Cumulative amenorrhea profiles and the incidence of bleeding or spotting Secondary: Not reported	Primary: Cumulative amenorrhea profiles for subjects treated with BZA 20 or 40 mg with CEE 0.625 or 0.45 mg were similar to those observed for placebo-treated subjects during the first and second year of therapy and were similar to those with raloxifene 60 mg during year one of treatment, with the exception of a lower rate of amenorrhea during cycles one through 13 for BZA 20 mg/CEE 0.45 mg compared to raloxifene 60 mg (83 vs 88%, respectively; P<0.05). Treatment with BZA 20 or 40 mg with CEE 0.625 or 0.45 mg was associated with a low incidence of bleeding or spotting events that was not significantly different compared to placebo. Secondary: Not reported
Lindsay et al. ¹⁴⁰ (2009) SMART-1 Single tablets of BZA (10, 20, or 40 mg), each with CEE (0.625 or 0.45 mg) daily vs raloxifene 60 mg daily	AC, DB, MC, PC, RCT Healthy, postmenopausal women age 40 to 75 with an intact uterus Osteoporosis Prevention I Substudy: Women >5 years postmenopause (N=1,454)	N=3,397 2 years	Primary: Change in BMD of the lumbar spine at month 12 Secondary: BMD of the hip, bone turnover biomarkers (BTM)	Primary: In substudies I and II, all BZA/CEE doses significantly increased (P<0.001) the adjusted mean percent change in BMD from baseline to 12 and 24 months vs decreases observed with placebo. Compared to raloxifene, the percent increase in lumbar spine BMD from baseline to month 24 was significantly higher for all BZA/CEE treatment groups (P<0.05) for women one to five years postmenopause. Among women >5 years postmenopause, BMD significantly improved relative to raloxifene (P<0.05) for all BZA/CEE doses, except those with BZA (40 mg). Secondary: In substudy I, total hip BMD was significantly higher (P<0.001) with all BZA/CEE doses from baseline to months 12 and 24 compared to the decreases observed with placebo. Compared to raloxifene, mean percent

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo taken daily	Osteoporosis Prevention II Substudy: Women 1 to 5 years postmenopause (N=861)			<p>increases in total hip BMD were significantly higher (P<0.05) from baseline to month 24 with BZA (10 mg)/CEE (0.625 or 0.45 mg) and BZA (20 mg)/CEE (0.625 mg). In substudy II, all BZA/CEE doses were significantly higher (P<0.01) for total hip BMD than with placebo at months 12 and 24. Total hip BMD was significantly better (P<0.05) than with raloxifene for BZA (10 mg)/CEE (0.625 or 0.45 mg), and BZA (20 mg)/CEE (0.45 mg) at month 24.</p> <p>In substudy II, at all time points, median percent changes from baseline in serum osteocalcin and C-telopeptide were significantly greater with all BZA/CEE doses than with placebo (P<0.001).</p>
<p>Pinkerton et al.¹⁴¹ (2009) SMART-2</p> <p>BZA 20 mg/CEE 0.45 mg once daily</p> <p>vs</p> <p>BZA 20 mg/CEE 0.625 mg once daily</p> <p>vs</p> <p>placebo once daily</p>	<p>DB, MC, PC, RCT</p> <p>Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, with moderate to severe hot flashes (≥7/day or 50/week)</p>	<p>N= 332</p> <p>12 weeks</p>	<p>Primary: Changes from baseline in the average daily number of moderate and severe hot flushes and the severity of hot flushes at weeks 4 and 12</p> <p>Secondary: Participants who had at least a 50% or 75% reduction in the number of hot flushes from baseline, time to reach a 50% decrease from baseline in the number of hot flushes for at least 3 consecutive days, the MOS sleep scale, Menopause-</p>	<p>Primary: All groups demonstrated a significant reduction (P<0.001) from baseline for the mean daily number of moderate and severe hot flushes at all time points. At weeks four and 12, these decreases were significantly greater with both BZA/CEE doses than with placebo (P<0.001). At week 12, BZA 20 mg/CEE 0.45 mg and BZA 20 mg/CEE 0.625 mg reduced hot flushes from baseline by 74% (10.3 [baseline] vs 2.8 [week 12]) and 80% (10.4 vs 2.4), respectively, compared to 51% (10.5 vs 5.4) for placebo. Similarly, the mean daily severity of hot flushes significantly improved (P<0.001) from baseline with BZA 20 mg/CEE 0.45 or 0.625 mg at all time points.</p> <p>Secondary: Overall, significantly more (P<0.001) BZA/CEE-treated women responded at both the 75% and 50% level compared to placebo at weeks four and 12. Significantly more women taking BZA 20 mg/CEE 0.625 mg compared to BZA 20 mg/CEE 0.45 mg were 75% responders. Similarly at weeks four and 12, significantly more participants treated with BZA/CEE than with placebo had at least a 75% (P<0.01) or 50% (P<0.001) decrease when mild, moderate, and severe hot flushes were assessed. The median time to reach a 50% reduction in hot flushes for at least three consecutive days was significantly shorter for BZA 20 mg/CEE 0.45 mg (15 days) and BZA 20 mg/CEE 0.625 mg (14 days) compared to placebo (30 days; P≤0.001).</p> <p>Compared to placebo-treated participants, those receiving BZA/CEE treatment had significant improvements from baseline (P<0.001) at week</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Specific Quality of Life (MENQOL), and the presence of breast pain	12 for time to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices I and II, as assessed by the MOS sleep scale. A significant improvement ($P<0.010$) in the number of hours slept each night was also observed in participants taking BZA 20 mg/CEE 0.625 mg compared to placebo.
Utian et al. ¹⁴² (2009) SMART-2 BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs placebo once daily	DB, MC, PC, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, with moderate to severe hot flushes (≥ 7 /day or 50/week)	N= 332 12 weeks	Primary: Medical Outcomes Study (MOS) sleep scale and Menopause- Specific Quality of Life (MENQOL) questionnaires and the Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ) Secondary: Not reported	Primary: At Week 12, both doses of BZA/CEE showed significant improvements ($P<0.001$) in scores for time to fall asleep, sleep disturbance, sleep adequacy, and sleep problems indexes I and II compared to placebo. Both BZA/CEE treatment groups showed significant improvements in vasomotor and total scores on the MENQOL questionnaire relative to placebo ($P<0.001$). Results of the MS-TSQ showed that BZA/CEE-treated subjects reported significantly greater satisfaction compared to placebo-treated subjects in the following 4 categories: ability to control hot flushes during the day ($P<0.001$) and night ($P<0.001$), effect on quality of sleep ($P<0.001$), and effect on mood or emotions ($P<0.05$).
Yu et al. ¹⁴³ (2013) SMART-2 BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs	DB, MC, PC, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, with moderate to severe hot flushes (≥ 7 /day or 50/week)	N= 332 12 weeks	Primary: Number of days per week without hot flushes from baseline to week 12, percentage of women who experienced no hot flushes at week 12 Secondary: Not reported	Primary: From baseline to week 12, the mean number of days per week without moderate-to-severe hot flushes steadily increased for both doses of BZA/CEE compared to placebo. These effects were significant for both doses starting at week three ($P<0.05$ for BZA 20 mg/CEE 0.45 mg and $P<0.01$ for BZA 20 mg/CEE 0.625 mg) and sustained through week 12. A significantly higher number of days per week without moderate-to-severe hot flushes was seen for BZA 20 mg/CEE 0.625 mg compared to BZA 20 mg/CEE 0.45 mg ($P<0.05$) starting at week four. At week 12, the mean number of days per week without moderate-to-severe hot flushes was higher for both BZA/CEE treatment groups (2.8 and 3.7 days for BZA 20 mg/CEE 0.45 and 0.625 mg, respectively) compared to the placebo group (1.0 days). Similarly, the mean number of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo once daily				<p>days without any hot flushes at week 12 was higher for the BZA/CEE treatment groups (1.8 and 2.8 days for BZA 20 mg/CEE 0.45 and 0.625 mg, respectively) than for the placebo group (0.6 days).</p> <p>At week 12, the percentage of women who had no moderate-to-severe hot flushes was significantly higher for both BZA/CEE doses compared to placebo (25.0% for BZA 20 mg/CEE 0.45 mg (P<0.01) and 40.6% for BZA 20 mg/CEE 0.625 mg (P<0.001) versus 5.8% for placebo.</p> <p>Secondary: Not reported</p>
<p>Kagan et al.¹⁴⁴ (2010) SMART-3</p> <p>BZA 20 mg/CEE 0.45 mg once daily</p> <p>vs</p> <p>BZA 20 mg/CEE 0.625 mg once daily</p> <p>vs</p> <p>BZA 20 mg once daily</p> <p>vs</p> <p>placebo once daily</p>	<p>AC, DB, MC, PC, RCT</p> <p>Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, vaginal cytological smear showing vaginal pH >5.0, and moderate to severe symptoms of vulvovaginal atrophy at screening</p>	<p>N=652</p> <p>12 weeks</p>	<p>Primary: Proportion of vaginal superficial cells, proportion of parabasal cells, vaginal pH, severity of the most bothersome vulvar/vaginal symptom at 12 weeks</p> <p>Secondary: Not reported</p>	<p>Primary: Mean increases in percentage of superficial cells from baseline to week 12 were significantly greater with BZA 20 mg/CEE 0.625 or 0.45 mg compared to placebo (P<0.01) and BZA 20 mg (P<0.001). Mean decreases from baseline to week 12 in percentage of parabasal cells were also significantly greater with both BZA/CEE doses than with placebo (P<0.001) or BZA 20 mg (P<0.001). Mean vaginal pH significantly decreased from baseline to week 12 with both BZA/CEE doses (P<0.001). No significant change from baseline was observed with placebo or BZA 20 mg. The mean vaginal pH decrease was significantly lower than that of the placebo group for the BZA 20 mg/CEE 0.625 group (P<0.001) but not the BZA 20 mg/CEE 0.45 mg group (P<0.116). Compared to BZA 20 mg, the mean vaginal pH change at week 12 was significantly lower than that with both BZA/CEE doses (P<0.001).</p> <p>At week 12, participants treated with BZA 20 mg/CEE 0.625 mg, but not those treated with BZA 20 mg/CEE 0.45 mg, had significantly greater improvements in their most bothersome symptom compared to participants treated with placebo (P=0.048). The most bothersome symptom improved significantly more with both BZA/CEE doses compared to BZA 20 mg at week 12.</p>
<p>Bachmann et al.¹⁴⁵ (2010) SMART-3</p> <p>BZA 20 mg/CEE</p>	<p>AC, DB, MC, PC, RCT</p> <p>Healthy postmenopausal</p>	<p>N=652</p> <p>12 weeks</p>	<p>Primary: Arizona Sexual Experiences (ASEX) Scale, Menopause-</p>	<p>Primary: Treatment with BZA 20 mg/CEE 0.45 or 0.625 mg was associated with improvement in sexual function at week 12, based on individual item scores and the total ASEX score. Compared to BZA 20 mg, there was significant improvement in total ASEX scores with BZA/CEE at week 12</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs BZA 20 mg once daily vs placebo once daily</p>	<p>women, 40 to 65 years of age with an intact uterus, vaginal cytological smear showing vaginal pH >5.0, and moderate to severe symptoms of vulvovaginal atrophy at screening</p>		<p>Specific Quality of Life (MENQOL) questionnaire, and Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ) Secondary: Not reported</p>	<p>(p<0.001), as well as in scores for ease of arousal, orgasm, and lubrication (p<0.05). Both doses of BZA/CEE significantly improved vasomotor function, sexual function and total scores on the MENQOL questionnaire at week 12 compared to placebo or BZA 20 mg (p<0.05). Subjects treated with BZA 20 mg/CEE 0.625 mg also reported significant improvement in physical function scores compared to placebo (p<0.05). Subjects in the BZA/CEE treatment groups reported significantly greater overall satisfaction on the MS-TSQ compared to subjects in the placebo group (p<0.05) or the BZA 20-mg group (p<0.001). Secondary: Not reported</p>
<p>Mirkin et. al.¹⁴⁶ (2013) SMART-4 BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs CEE 0.45 mg/MPA 1.5 mg once daily vs</p>	<p>DB, MC, PC, AC, PG, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus</p>	<p>N= 1,061 12 months</p>	<p>Primary: Endometrial hyperplasia, lumbar spine BMD Secondary: Hip BMD, amenorrhea, breast pain</p>	<p>Primary: At one year, no cases of endometrial hyperplasia were identified in the BZA 20 mg/CEE 0.45 mg group, while three cases (1.1%) were confirmed for the BZA 20 mg/CEE 0.625 mg group. All active treatment groups showed significant increases from baseline in lumbar spine BMD at one year (P<0.001) compared to placebo, which showed significant decreases from baseline (P<0.001). The increases for BZA 20 mg/CEE 0.45 and 0.625 mg were significantly greater than those for placebo (P<0.001 for all) but were significantly less than those observed for CEE 0.45 mg/MPA 1.5 mg (P<0.001). Secondary: For BMD at the total hip, BZA 20 mg/CEE 0.45 and 0.625 mg showed significantly greater increases from baseline compared to placebo (P<0.001). The increase for BZA 20 mg/CEE 0.625 mg was not statistically different from that for CEE 0.45 mg/MPA 1.5 mg. Based on subject daily diary reporting, both BZA/CEE groups showed high rates of cumulative amenorrhea over one year of treatment (ranges of 85.3 to 99.2% and 82.9 to 96.5% for BZA 20 mg/CEE 0.45 and 0.625 mg,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo once daily</p>				<p>respectively). These rates were generally similar to those for placebo (82.0 to 95.4%) but were significantly higher than those for CEE 0.45 mg/MPA 1.5 mg (48.9 to 83.2%; $P<0.001$).</p> <p>The percentage of subjects in the BZA/CEE treatment groups who reported ≥ 1 day of breast pain during 4-week cycles over the first three months of therapy (ranges of 5.7 to 9.2% and 5.0 to 6.7% for BZA 20 mg/CEE 0.45 and 0.625 mg, respectively) was similar to that for placebo (4.6 to 9.8%). Compared to CEE 0.45 mg/MPA 1.5 mg (13.3 to 14.6%), significantly lower incidences of breast pain were observed for BZA 20 mg/CEE 0.45 mg (weeks 5 to 8 and 9 to 12; $P<0.05$) and for BZA 20 mg/CEE 0.625 mg (weeks 1 to 4, 5 to 8, and 9 to 12; $P<0.01$).</p>
<p>Pinkerton et al.¹⁴⁷ (2013) SMART-5</p> <p>BZA 20 mg/CEE 0.45 mg once daily</p> <p>vs</p> <p>BZA 20 mg/CEE 0.625 mg once daily</p> <p>vs</p> <p>BZA 20 mg once daily</p> <p>vs</p> <p>CEE 0.45 mg/MPA 1.5 mg once daily</p> <p>vs</p>	<p>DB, MC, PC, AC, PG, RCT</p> <p>Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, no endometrial hyperplasia or breast cancer at screening or use of HT or SERM-containing medications within eight weeks of screening.</p>	<p>N= 1,843 (N=940 for breast density substudy)</p> <p>12 months</p>	<p>Primary: Change from baseline in percent dense breast tissue</p> <p>Secondary: Not reported</p>	<p>Primary: At 12 months, there were no significant differences between the BZA-CE or BZA and placebo groups in change from baseline in percent dense breast tissue as determined by mammography. The CEE-MPA group demonstrated a significant ($P<0.001$) increase in percent dense breast tissue compared to placebo in the modified intent-to-treat population. BZA 20 mg-conjugated estrogens 0.45 and 0.625 mg demonstrated noninferiority compared to placebo in the change from baseline in percent dense breast tissue at 12 months.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo once daily</p> <p>Pinkerton et al.¹⁴⁸ (2014) SMART-5</p> <p>BZA 20 mg/CEE 0.45 mg once daily</p> <p>vs</p> <p>BZA 20 mg/CEE 0.625 mg once daily</p> <p>vs</p> <p>BZA 20 mg once daily</p> <p>vs</p> <p>CEE 0.45 mg/MPA 1.5 mg once daily</p> <p>vs</p> <p>placebo once daily</p>	<p>DB, MC, PC, AC, PG, RCT</p> <p>Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, no endometrial hyperplasia or breast cancer at screening or use of HT or SERM-containing medications within eight weeks of screening.</p>	<p>N= 1,843</p> <p>12 months</p>	<p>Primary: BMD at 12 months, endometrial hyperplasia at 12 months, breast density at 12 months</p> <p>Secondary: Cumulative amenorrhea, breast pain</p>	<p>Primary: CEE 0.45 mg/BZA 20 mg, BZA 20 mg, and CEE 0.45 mg/MPA 1.5 mg significantly increased lumbar spine, total hip, and femoral neck BMD compared to placebo (P<0.01 for all) and showed significantly greater decreases from baseline in serum bone turnover markers compared to placebo (P<0.01 for all) at 12 months. There were no differences among groups in the incidence of fractures.</p> <p>Rates of endometrial hyperplasia were <1% and similar for CEE 0.45 mg/BZA 20 mg, BZA 20 mg, CEE 0.45 mg/MPA 1.5 mg, and placebo. CEE 0.45 mg/BZA 20 mg (P<0.05) and CEE 0.45 mg/MPA 1.5 mg (P<0.001) showed significantly greater increases from baseline in endometrial thickness compared to placebo.</p> <p>Secondary: The percentage of subjects reporting at least one day of breast tenderness was similar for CEE 0.45 mg/BZA 20 mg, BZA alone, and placebo but significantly lower than that for CEE/MPA (P<0.001 versus placebo and P<0.01 versus CEE/BZA or BZA alone for all time periods).</p> <p>Rates of cumulative amenorrhea were similar for CEE 0.45 mg/BZA 20 mg, BZA 20 mg, and placebo over one year of treatment and significantly higher than those for CEE/MPA at each time point (P<0.001). Incidences of adverse events and treatment-emergent adverse events were similar with CEE/BZA and placebo; more subjects in the CEE/MPA group discontinued the study due to adverse events compared to other groups.</p>
<p>Pinkerton et al.¹⁴⁹ (2014)</p> <p>BZA 20mg/CEE 0.45</p> <p>vs</p>	<p>PH</p> <p>Subgroups of women from the SMART-1 and SMART-2 trials who were either <5 or ≥5 years since</p>	<p>N=1,592</p> <p>12 weeks</p>	<p>Primary: Frequency and severity of hot flashes, health-related quality of life (HRQoL), sleep, satisfaction with treatment,</p>	<p>Primary: In both the SMART-1 and SMART-2 trials, BZA 20mg/CEE 0.45 and 0.625 mg treatment showed a significantly greater decrease in the average daily number of moderate-to-severe hot flashes in both the <5 and ≥5 YSM subgroups at three months compared to placebo.</p> <p>The BZA 20 mg/CEE 0.45 and 0.625 mg groups in both studies showed significantly greater improvement from baseline in total MENQOL scores</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>BZA 20mg/CEE 0.625 mg</p> <p>vs</p> <p>placebo</p>	<p>menopause (YSM)</p>		<p>cumulative amenorrhea, and breast pain</p> <p>Secondary: Not reported</p>	<p>at three months compared to placebo ($P \leq 0.05$). There was no difference between subjects who were <5 or ≥ 5 YSM.</p> <p>In the SMART-1 trial, both the <5 and ≥ 5 YSM subgroups showed significant improvement from baseline in some sleep parameters with BZA/CEE treatment compared to placebo at three months. Similarly, in the SMART-2 trial, both BZA/CEE doses showed significantly greater improvement from baseline in various sleep parameters for the <5 and ≥ 5 YSM subgroups compared to placebo at three months.</p> <p>Satisfaction with treatment was assessed in the SMART-2 trial. BZA 20 mg/ CEE 0.45 and 0.625 mg improved subjects' satisfaction with treatment compared to placebo in both the <5 and ≥ 5 YSM subgroups. A significantly greater percentage of BZA/CEE-treated subjects in both the <5 and ≥ 5 YSM subgroups were satisfied with treatment overall (range, 69 to 83%) at month three compared to placebo (range, 32 to 51%; $P < 0.05$).</p> <p>Overall, treatment with BZA 20mg/CEE 0.45 and 0.625 mg in the SMART-1 and SMART-2 trials was associated with low rates of breast pain (range, 2 to 13%), similar to that for placebo (range, 0 to 9%), in both subgroups.</p> <p>Secondary: Not reported</p>
<p>Komm et al.¹⁵⁰ (2015) SMART trials</p> <p>BZA 20 mg/CEE 0.45 mg once daily</p> <p>vs</p> <p>BZA 20 mg/CEE 0.625 mg once daily</p>	<p>MA of the SMART trials</p> <p>Healthy, non-hysterectomized, postmenopausal women</p>	<p>N=6109</p> <p>Up to 2 years</p>	<p>Primary: VTEs, CHD, and cerebrovascular events</p> <p>Secondary: Not reported</p>	<p>Primary: The incidence of VTEs with CE 0.45 mg/BZA 20 mg was low (0.2%) and similar to placebo (0.1%), as was the incidence in the group of women given any dose of CE/BZA (0.1%). There were no VTEs in any participants given CE 0.625 mg/BZA 20 mg.</p> <p>Stroke occurred in one (0.06%) participant in the CE 0.45 mg/BZA 20 mg group, one ($<0.06\%$) in the CE 0.625 mg/BZA 20 mg group, and four (0.08%) among all participants who received any CE/BZA dose. There were two adjudicated TIAs in the CE 0.45 mg/BZA 20 mg group and eight (0.2%) among participants treated with any CE/BZA dose. None occurred in the CE 0.625 mg/BZA 20 mg or placebo groups.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs BZA/CEE any dose vs placebo				Adjudicators confirmed CHD events in four (0.3%) participants given CE 0.45 mg/BZA 20 mg, four (0.3%) given CE 0.625 mg/BZA 20 mg, a total of 14 (0.3%) given any CE/BZA dose, and three (0.2%) with placebo. Rates of MI were 0.2%, 0.1%, 0.1%, and 0.2%, respectively. Secondary: Not reported

*Estradot[®] is marketed in the United States as Vivelle-Dot[®].

†Menorest[®] is marketed in the United States as Vivelle[®].

‡Product is not available in the United States.

Study design abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PH=post-hoc analysis, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=cross-over

Miscellaneous abbreviations: 3MSE= Modified Mini-Mental State Examination, AIP=atherogenic index of plasma, AUC=area under the curve, BMD=bone mineral density, BP=blood pressure, BZA=bazedoxifene, CABG= coronary artery bypass graft, CBG=cortisol binding globulin, CEE=conjugated equine estrogen, CHD=coronary heart disease, CHF= congestive heart failure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, FI=fluctuation index, FSH= follicle-stimulating hormone, HDL-C= high-density lipoprotein cholesterol, HR=hazard ratio, HOMA-IR=homeostasis model assessment of insulin resistance, ICAM=intracellular adhesion molecule, IGF-1=insulin-like growth factor 1, IL-6=interleukin-6, LDL-C= low-density lipoprotein cholesterol, MI=myocardial infarction, MPA=medroxyprogesterone, OR=odds ratio, PCI= percutaneous coronary interventions, PE=pulmonary embolism, QCT=quantitative computed tomography, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, SHBG=sex hormone binding globulin, SMART= selective estrogens, menopause, and response to therapy trials, TBG=thyroxine binding globulin, TC=total cholesterol, TG=triglyceride, VLDL-C=very-low-density lipoprotein cholesterol, VTE=venous thromboembolism, WHI=Women's Health Initiative, WHIMS=Women's Health Initiative Memory Study

Additional Evidence

Dose Simplification

Two studies demonstrated that continuous administration of hormone therapy was better tolerated than sequential administration, which led to an improvement in compliance. Doren et al. found that women who were treated with continuous estrogen and progestin therapy (estradiol 2 mg, estriol 1 mg, and norethisterone 1 mg) had better compliance than women who were treated sequentially with estradiol valerate 2 mg daily and medroxyprogesterone acetate 5 mg daily for 12 days of the month (93 vs 66%, respectively). The most frequent reason for discontinuation of therapy was uterine bleeding.¹⁵¹ Eiken et al. found that the continuous administration of estradiol and norethisterone improved compliance compared to the sequential administration of the same product. The eight year compliance rate for the continuous combination regimen was 46% compared to 32% for the sequential regimen. The difference in compliance rates was due to monthly bleeding associated with the sequential regimen.¹⁵²

Stable Therapy

Place et al. evaluated women whose menopausal symptoms were satisfactorily controlled on conjugated estrogens. Participants were randomly selected to continue with oral therapy or to switch to transdermal estradiol. The results showed that women who switched to transdermal therapy had similar relief of menopausal symptoms as the women who remained on oral conjugated estrogens.⁸²

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 12. Relative Cost of the Estrogens

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Estradiol	tablet, topical gel, topical spray, transdermal patch, vaginal cream, vaginal ring, vaginal tablet	Alora [®] , Climara [®] *, Divigel [®] , Elestrin [®] , Estrace [®] *, Estring [®] , Evamist [®] , Menostar [®] , Minivelle [®] *, Vagifem [®] *, Vivelle-Dot [®] *	\$\$\$\$\$	\$
Estradiol acetate	vaginal ring	Femring [®]	\$\$\$\$\$	N/A
Estradiol cypionate	injection	Depo-Estradiol [®]	\$\$\$\$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Estradiol valerate	injection	Delestrogen ^{®*}	\$\$	\$\$\$
Estradiol and drospirenone	tablet	Angeliq [®]	\$\$\$\$	N/A
Estradiol and levonorgestrel	transdermal patch	Climara Pro [®]	\$\$\$\$	N/A
Estradiol and norethindrone	tablet, transdermal patch	Activella ^{®*} , Amabelz ^{®*} , Combipatch [®] , Mimvey ^{®*}	\$\$\$	\$\$\$
Estradiol and norgestimate	tablet	Prefest [®]	\$\$\$\$	N/A
Estrogens, conjugated	injection, tablet, vaginal cream	Premarin [®]	\$\$\$\$	N/A
Estrogens, conjugated, synthetic B	tablet	Enjuvia [®]	\$\$\$	N/A
Estrogens, conjugated and bazedoxifene	tablet	Duavee [®]	\$\$\$\$	N/A
Estrogens, conjugated and medroxyprogesterone	tablet	Premphase [®] , Prempro [®]	\$\$\$\$	N/A
Estrogens, esterified	tablet	Menest [®]	\$\$\$	N/A
Estropipate	tablet	N/A	N/A	\$
Norethindrone and ethinyl estradiol	tablet	FemHRT ^{®*} , Jevantique ^{®*} , Jinteli ^{®*}	\$\$\$	\$\$\$

*Generic is available in at least one dosage form or strength.

N/A=Not available

X. Conclusions

The estrogens are approved for the treatment of vasomotor symptoms associated with menopause, vulvar and vaginal atrophy, abnormal uterine bleeding, hypoestrogenism, prevention of postmenopausal osteoporosis, as well as for the palliative treatment of prostate and breast cancer.¹⁻³² They are available in a variety of dosage forms, including injectable, oral, topical, transdermal, and vaginal preparations. Estradiol, estradiol valerate, estradiol-norethindrone, estropipate, and norethindrone-ethinyl estradiol are available in a generic formulation.

The recommendations for the use of hormone therapy have changed since the Women's Health Initiative studies were published.³³⁻⁴⁵ The use of hormone therapy was associated with an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis.⁴⁷⁻⁴⁸ The long-term use of hormone therapy is no longer recommended for the prevention of chronic diseases, such as cardiovascular disease, cerebrovascular disease, or dementia.^{35,41-44} Hormone therapy may be considered for the prevention of osteoporosis when other therapies are not appropriate or when the benefits outweigh the risks.^{34-35,42} Hormone therapy remains the most effective treatment for moderate-to-severe menopausal symptoms.^{34-35,37,42}

It is recommended that the lowest possible dose be used for the shortest amount of time.^{33-35,41-42} Vaginal formulations are recommended for women who only have symptoms of vulvar and vaginal atrophy.^{35,39,42} Systemic progestogen is required for endometrial protection of unopposed estrogen therapy.^{33,35,41-42}

A variety of clinical trials have been conducted with the estrogens, which have evaluated efficacy, safety, tolerability, as well as pharmacokinetic and pharmacodynamic end points. Numerous studies have demonstrated a similar improvement in menopausal symptoms with the various estrogen preparations.^{35-36,39,70,72,76,78-86,89-91,95-98,102,124} There were no studies found in the medical literature that compared the continuous administration of a combination product versus the concomitant administration of the individual components. There is no evidence that natural estrogens are more or less hazardous than synthetic estrogens at equivalent doses.¹⁻³²

The efficacy and safety of bazedoxifene with conjugated estrogens have been evaluated in the phase 3 Selective estrogens, Menopause And Response to Therapy (SMART) trials conducted in generally healthy postmenopausal

women.¹³⁷⁻¹⁴⁸ Bazedoxifene-conjugated estrogens have shown an improvement in menopausal symptoms and bone loss and a favorable safety profile when compared to placebo.¹³⁷⁻¹⁵⁰ There were no studies found that compared bazedoxifene-conjugated estrogens to another selective estrogen receptor modifier and estrogen combination regimen.

There is insufficient evidence to support that one brand estrogen is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand estrogen is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2017 Jan]. Available from: <http://www.thomsonhc.com/>.
2. Alora[®] [package insert]. Parsippany (NJ): Actavis Pharma, Inc.; 2013 Nov.
3. Climara[®] [package insert]. Wayne (NJ): Bayer HealthCare Pharmaceuticals Inc.; 2013 Oct.
4. Delestrogen[®] [package insert]. Spring Valley (NY): Par Pharmaceutical Companies, Inc.; 2014 Sep.
5. Depo-Estradiol[®] [package insert]. New York (NY): Pharmacia & Upjohn Co.; 2005 Jun.
6. Divigel[®] [package insert]. Minneapolis (MN): Upsher-Smith Laboratories, Inc.; 2012 May.
7. Elestrin[®] [package insert]. San Antonio (TX): DPT Laboratories, Ltd.; 2014 Feb.
8. Enjuvia[®] [package insert]. North Wales (PA): Teva Pharmaceuticals USA, Inc.; 2015 Jun.
9. Estrace[®] tablet [package insert]. Irvine (CA): Allergan; 2016 May.
10. Estrace[®] vaginal cream [package insert]. Rockaway (NJ): Warner Chilcott (US), LLC; 2011 Dec.
11. Estring[®] [package insert]. New York (NY): Pfizer, Inc.; 2015 Sep.
12. Estropipate [package insert]. Corona (CA): Watson Pharma, Inc.; 2012 Jul.
13. Evamist[®] [package insert]. San Antonio (TX): DPT Laboratories, Ltd; 2014 Mar.
14. Femring[®] [package insert]. Rockaway (NJ): Warner Chilcott (US), LLC.; 2014 May.
15. Menest[®] [package insert]. Bristol (TN): King Pharmaceuticals, Inc.; 2011 Sep.
16. Menostar[®] [package insert]. Wayne (NJ): Bayer HealthCare Pharmaceuticals Inc.; 2012 Apr.
17. Premarin[®] injection [package insert]. Philadelphia (PA): Wyeth Pharmaceuticals, Inc; 2012 Apr.
18. Premarin[®] tablet [package insert]. Philadelphia (PA): Wyeth Pharmaceuticals Inc; 2014 Dec.
19. Premarin[®] vaginal cream [package insert]. Philadelphia (PA): Wyeth Pharmaceuticals Inc; 2015 Dec.
20. Vagifem[®] [package insert]. Princeton (NJ): Novo Nordisk Inc.; 2012 Apr.
21. Vivelle-Dot[®] [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2014 Jul.
22. Minivelle[®] [package insert]. Miami (FL): Noven Pharmaceuticals, Inc.; 2014 Sep.
23. Activella[®] [package insert]. Plainsboro (NJ): Novo Nordisk; 2013 Oct.
24. Angeliq[®] [package insert]. Wayne (NJ): Bayer Healthcare Pharmaceuticals Inc.; 2015 Jun.
25. Climara Pro[®] [package insert]. Wayne (NJ): Bayer HealthCare Pharmaceuticals, Inc; 2013 Oct.
26. Combipatch[®] [package insert]. Miami (FL): Noven Pharmaceuticals, Inc.; 2015 May.
27. Femhrt[®] [package insert]. Rockaway (NJ): Warner Chilcott (US), LLC; 2014 Jan.
28. Jinteli[®] [package insert]. North Wales (PA): Teva Pharmaceuticals, USA; 2016 Feb.
29. Mimvey[®] [package insert]. North Wales (PA): TEVA Pharmaceuticals USA Inc; 2016 Jul.
30. Prefest[®] [package insert]. North Wales (PA): Teva Women's Health, Inc.; 2016 Feb.
31. Premphase[®] and Prempro[®] [package insert]. Philadelphia (PA): Wyeth Pharmaceuticals Inc; 2011 May.
32. Duavee[®] [package insert]. Philadelphia (PA): Wyeth Pharmaceuticals Inc; 2015 Sep.
33. de Villiers TJ, Hall JE, Pinkerton JV, et al. Revised Global Consensus Statement on Menopausal Hormone Therapy. *Climacteric*. 2016 Aug;19(4):313-5.
34. No authors listed. Management of osteoporosis in postmenopausal women: 2010 position statement of the North American Menopause Society. *Menopause*. 2010 Jan-Feb;17(1):23-54.
35. North American Menopause Society. Position statement: The 2012 hormone therapy position statement of the North American Menopause Society. *Menopause* 2012; 19(3):257-271.
36. North American Menopause Society. The North American Menopause Society Statement on Continuing Use of Systemic Hormone Therapy After Age 65. *Menopause*. 2015 Jul;22(7):693.
37. Armeni E, Lambrinoudaki I, Ceausu I, et al. Maintaining postreproductive health: A care pathway from the European Menopause and Andropause Society (EMAS). *Maturitas*. 2016 Jul;89:63-72.
38. National Osteoporosis foundation. Clinician's guide to prevention and treatment of osteoporosis [guideline on the Internet]. Washington (DC): National Osteoporosis Foundation; 2014 [cited 2014 Sep]. Available from: <http://nof.org/files/nof/public/content/file/2791/upload/919.pdf>.
39. North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause*. 2013;20(9):888-902.
40. Mosca L, Banka CL, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women- 2011 update: A guideline from the American Heart Association. *Circulation*. 2011;123:1243-1262.
41. Baber RJ, Panay N, Fenton A; IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric*. 2016 Apr;19(2):109-50.

42. Goodman NF, Cobin RH, Ginzburg SB, Katz IA, Woode DE. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. *Endocr Pract.* 2011 Nov/Dec;17(Suppl 6):1-25.
43. Moyer VA; US Preventive Services Task Force. Menopausal hormone therapy for the primary prevention of chronic conditions: US Preventative Services Task Force recommendation statement. *Ann Intern Med.* 2013;158:47-54.
44. Hormone therapy and heart disease. Committee Opinion No. 565. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2013;121:1407-10.
45. Royal College of Obstetricians and Gynaecologists (RCOG). Venous thromboembolism and hormone replacement therapy (Green-top 19) [guideline on the Internet]. London (UK): RCOG; 2011 May [cited 2016 Dec]. Available from: <http://www.rcog.org.uk/womens-health/clinical-guidance/hormone-replacement-therapy-and-venous-thromboembolism-green-top-19>.
46. Manson JE, Martin KA. Postmenopausal hormone-replacement therapy. *N Engl J Med.* 2001 Jul 5;345(1):34-40.
47. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principle results from the Women's Health Initiative randomized controlled trials. *JAMA.* 2002;288:321-33.
48. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004 Apr 14;291(14):1701-12.
49. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and estrogen/progestin replacement study follow-up (HERS II). *JAMA.* 2002 Jul 3;288(1):49-57.
50. Estrogen and estrogen with progestin therapies for postmenopausal women [internet]. Rockville (MD): Food and Drug Administration (US): 2010 Jun [cited 2016 Sep]. Available from: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135318.htm>.
51. Questions and answers for estrogen and estrogen with progestin therapies for postmenopausal women (updated) [internet]. Rockville (MD): Food and Drug Administration (US): 2009 Apr [cited 2016 Sep]. Available from: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339.htm>.
52. Martin KA, Barbieri RL. Preparations for menopausal hormone therapy. In: *UpToDate*, Snyder PJ and Crowley WF (Ed), *UpToDate*, Waltham, MA, 2017.
53. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Jan 2017]. Available from: <http://online.factsandcomparisons.com>.
54. Stefanick ML, Anderson GL, Margolis KL, Hendrix SL, Rodabough RJ, Paskett ED, et al; WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA.* 2006 Apr 12;295(14):1647-57.
55. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease. *Arch Intern Med.* 2006;166:357-65.
56. Chlebowski RT, Anderson GL, Sarto GE, et al. Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial. *J Natl Cancer Inst.* 2015 Dec 14;108(3).
57. LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al. Health Outcomes After Stopping Conjugated Equine Estrogens Among Postmenopausal Women With Prior Hysterectomy. A Randomized Controlled Trial. *JAMA.* 2011;305(13):1305-14.
58. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA.* 2004;291(24):2959-68.
59. Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med.* 2006;166:357-65.
60. Jackson RD, Wactawski-Wende J, LaCroix AZ, Pettinger M, Yood RA, Watts NB, et al. Women's Health Initiative Investigators. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. *J Bone Miner Res.* 2006 Jun;21(6):817-28.
61. Schaeffers M, Muysers C, Alexandersen P, Christiansen C. Effect of microdose transdermal 17beta-estradiol compared with raloxifene in the prevention of bone loss in healthy postmenopausal women: a 2-year, randomized, double-blind trial. *Menopause.* 2009 May-Jun;16(3):559-65.
62. Haines C, Yu SL, Heimeyer F, Schaeffers M. Micro-dose transdermal estradiol for relief of hot flushes in postmenopausal Asian women: a randomized controlled trial. *Climacteric.* 2009;12:419-26.

63. Buster JE, Koltun WD, Pascual ML, Day WW, Peterson C. Low-dose estradiol spray to treat vasomotor symptoms: a randomized controlled trial. *Obstet Gynecol.* 2008 June;111(6): 1343-51.
64. Hodis HN, Mack WJ, Henderson VW, et al. Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. *N Engl J Med.* 2016 Mar 31;374(13):1221-31.
65. Mizunuma H, Taketani Y, Ohta H, Honjo H, Gorai I, Itabashi A, et al. Dose effects of oral estradiol on bone mineral density in Japanese women with osteoporosis. *Climacteric.* 2010;13:72-83.
66. Good WR, John VA, Ramirez M, et al. Double-masked, multicenter study of an estradiol matrix transdermal delivery system (Alora™) versus placebo in postmenopausal women experiencing menopausal symptoms. *Clin Ther.* 1996;18(6):1093-105.
67. Bowen AJ, John VA, Ramirez ME, et al. Bioavailability of oestradiol from the Alora™ (0.1 mg/day) oestradiol matrix transdermal delivery system compared with Estraderm® (0.1 mg/day). *J Obstet Gynecol.* 1998;18(6):575-80.
68. Ibarra de Palacios P, Schmidt G, Sergejew T, et al. Comparative study to evaluate skin irritation and adhesion of Estradot and Climara in healthy postmenopausal women. *Climacteric.* 2002;5(4):383.
69. Archer DF, Pickar JH, Bottiglioni F. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. *Menopause Study Group. Obstet Gynecol.* 1994;83(5 Pt 1):686.
70. Archer DF, Furst K, Tipping D, et al. A randomized comparison of continuous combined transdermal delivery of estradiol-norethindrone acetate and estradiol alone for menopause. *Obstet Gynecol.* 1999;94:498-503.
71. Harrison LI, Harari D. An evaluation of bioequivalence of two 7-day 17β-estradiol transdermal delivery systems by anatomical site. *J Clin Pharmacol.* 2002;42:1134-41.
72. Pornel B, Genazzain AR, Costes D, et al. Efficacy and tolerability of Menorest® 50 compared with Estraderm® TTS 50 in the treatment of postmenopausal symptoms. A randomized, multicenter, parallel group study. *Maturitas.* 1995;22:207-18.
73. Toole J, Silagy S, Maric A, et al. Evaluation of irritation and sensitization of two 50 µg/day oestrogen patches. *Maturitas.* 2002;43:257-63.
74. Erianne JA, Winter L. Comparison of the local tolerability and adhesion of a new matrix system (Menorest®) for estradiol delivery with an established transdermal membrane system (Estraderm TTS®). *Maturitas.* 1997;26:95-101.
75. Andersson TLG, Stehle B, Davidsson B, et al. Bioavailability of estradiol from two matrix transdermal delivery systems: Menorest® and Climara®. *Maturitas.* 2000;34:57-64.
76. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev.* 2006 Oct 18;(4):CD001500.
77. Yang TS, Chen YJ, Liang WH, and et al. A clinical trial of 3 doses of transdermal 17b-estradiol for preventing postmenopausal bone loss: a preliminary study. *J Chin Med Assoc.* 2007 May;70(5):200-6.
78. Polvani F, Zichella L, Bocci A, et al. A randomized comparative study for the clinical evaluation of hormone replacement by transdermal and oral routes. *Clin Exp Obstet Gynecol.* 1991;18(4):207.
79. Cortellaro M, Nencioni T, Boschetti C, et al. Cyclic hormonal replacement therapy after the menopause: transdermal versus oral treatment. *Eur J Clin Pharmacol.* 1991;41(6):555.
80. Pattison NS, Uptin T, Knox B, et al. Transdermal oestrogen for postmenopausal women: a double blind crossover comparative study with ethinyl oestradiol. *Aust N Z J Obstet Gynaecol.* 1989;29(1):62.
81. Hirvonen E, Lipasti A, Malkonen M, et al. Clinical and lipid metabolic effects of unopposed oestrogen and two oestrogen-progestogen regimens in post-menopausal women. *Maturitas.* 1987;9(1):69.
82. Place VA, Powers M, Darley PE, et al. A double-blind comparative study of Estraderm and Premarin in the amelioration of postmenopausal symptoms. *Am J Obstet Gynecol.* 1985;152(8):1092.
83. Al-Azzawi F, Buckler HM for the United Kingdom Vaginal Ring Investigator Group. Comparison of a novel vaginal ring delivering estradiol acetate versus oral estradiol for relief of vasomotor menopausal symptoms. *Climacteric.* 2003;6(2):118.
84. Nachtigall LE. Clinical trial of the estradiol vaginal ring in the U.S. *Maturitas.* 1995;22:S43-7.
85. Hilditch JR, Lewis J, Ross AH, et al. A comparison of the effects of oral conjugated equine estrogen and transdermal estradiol-17β combined with an oral progestin on quality of life in postmenopausal women. *Maturitas.* 1996;24:177-84.
86. Blanc B, Cravello L, Micheletti M-C, et al. Continuous hormone replacement therapy for menopause combining nomegestrol acetate and gel, patch, or oral estrogen: a comparison of amenorrhea rates. *Clin Ther.* 1998;20(5):901-12.
87. Polatti F, Viazzo F, Colleoni R, et al. Uterine myoma in postmenopause: a comparison between two therapeutic schedules of HRT. *Maturitas.* 2000;37:27-32.

88. Jarvinen A, Backstrom A-C, Elfstrom C, et al. Comparative absorption and variability in absorption of estradiol from a transdermal gel and a novel matrix-type transdermal patch. *Maturitas*. 2001;38:189-96.
89. Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. *JAMA*. 2004;291(13):1610-20.
90. Studd JWW, McCarthy K, Zamblera D, et al. Efficacy and tolerance of Menorest[®] compared to Premarin[®] in the treatment of postmenopausal women. A randomized, multicentre, double-blind, double-dummy study. *Maturitas*. 1995;22:105-14.
91. Good WR, John VA, Ramirez M, et al. Comparison of Alora estradiol matrix transdermal delivery system with oral conjugated equine estrogen therapy in relieving menopausal symptoms. *Climacteric*. 1999;2(1):29-36.
92. Chetkowski RJ, Meldrum DR, Steingold KA, et al. Biologic effects of transdermal estradiol. *N Engl J Med*. 1986;14(25):1615.
93. Manonai J, Theppisai U, Suthutvoravut S, et al. The effect of estradiol vaginal tablet and conjugated estrogen cream on urogenital symptoms in postmenopausal women: a comparative study. *J Obstet Gynaecol Res*. 2001;27(5):255.
94. Slater CC, Hodis HN, Mack WJ, et al. Markedly elevated levels of estrone sulfate after long-term oral, but not transdermal, administration of estradiol in postmenopausal women. *Menopause*. 2001;8(3):200.
95. Pornel B. Efficacy and safety of Menorest in two positive-controlled studies. *Eur J Obstet Gynecol Reprod Biol*. 1996;64:S35.
96. Ayton RA, Darling GM, Murkies AL, et al. A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy. *Br J Obstet Gynaecol*. 1996;103(4):351.
97. Studd JW, MacCarthy K, Zamblera D, et al. Efficacy and safety of Menorest (50 mikrog/day) compared to Premarin 0.625 mg in the treatment of menopausal symptoms and the prevention of bone loss, in menopausal women. A single-center, comparative, randomized, double-blind, double-dummy study. *Scand J Rheumatol Suppl*. 1996;103:89.
98. Gordon SF, Thompson KA, Ruoff GE, et al. Efficacy and safety of a seven-day, transdermal estradiol drug-delivery system: comparison with conjugated estrogens and placebo. The Transdermal Estradiol Patch Study Group. *Int J Fertil Menopausal Stud*. 1995;40(3):126.
99. Shifren JL, Rifai N, Desindes S, McIlwain M, Doros G, Mazer NA. A comparison of the short-term effects of oral conjugated equine estrogens versus transdermal estradiol on c-reactive protein, other serum markers of inflammation, and other hepatic proteins in naturally menopausal women. *J Clin Endocrinol Metab*. 2008 May;93(5): 1702-10.
100. Vrablik M, Fait T, Kovar J, Poledne R, Ceska R. Oral but not transdermal estrogen replacement therapy changes the composition of plasma lipoproteins. *Metabolism*. 2008 Aug;57(8): 1088-92.
101. Gupta P, Ozel B, Stanczyk F, Felix J, Mishell D. The effect of transdermal and vaginal estrogen therapy on markers of postmenopausal estrogen status. *Menopause*. 2008 Jan-Feb;15(1): 94-7.
102. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev*. 2016 Aug 31;(8):CD001500.
103. Hulley S, Grady D, Bush T, et al. for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605-13.
104. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II). *JAMA*. 2002;288:58-66.
105. Maki PM, Gast MJ, Vieweg AJ, et al. Hormone therapy in menopausal women with cognitive complaints. *Neurology*. 2007;69:1322-30.
106. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;349:523-34.
107. Reeves GK, Ceral V, Green J et al. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol*. 2006;7:910-18.
108. Rossouw J, Prentice R, and Manson J, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297:1465-77.
109. Salpeter SR, Walsh JM, Ormiston TM and et al. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. *Diabetes Obes Metab*. 2006;8(5):538-54.
110. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA*. 2003;289:3243-53.

111. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med.* 2003;348(19):1839-54.
112. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative memory study: a randomized controlled trial. *JAMA.* 2003;289:2651-62.
113. Cravioto MDC, Durand-Carbajal M, Jimenez-Santana L, Lara-Reyes P, Seuc AH, Sanchez-Guerrero J. Efficacy of estrogen plus progestin in menopausal symptoms in women with systemic lupus erythematosus: a randomized, double-blind, controlled trial. *Arthritis Care & Research.* 2011;63(12):1654-63.
114. Van de Weijer PH, Sturdee DW, von Holst T. Estradiol and levonorgestrel: effects on bleeding pattern when administered in a sequential combined regimen with a new transdermal patch. *Climacteric.* 2002;5(1).
115. Sanada M, Tsuda M, Kodama I, et al. Substitution of transdermal estradiol during oral estrogen-progestin therapy in postmenopausal women: effects on hypertriglyceridemia. *Menopause.* 2004;11(3):331-6.
116. Chunha EP, Azevedo LH, Pomperi LM, Strufaldi R, Steiner ML, Ferreria JAS, et al. Effect of abrupt discontinuation vs gradual dose reduction of postmenopausal hormone therapy on hot flashes. *Climacteric.* 2010;13:362-7.
117. Simon JA, Liu JH, Speroff L, et al. Reduced vaginal bleeding in postmenopausal women who receive combined norethindrone acetate and low-dose ethinyl estradiol therapy versus combined conjugated equine estrogens and medroxyprogesterone acetate therapy. *Am J Obstet Gynecol.* 2003;188:92-9.
118. Simon JA, Symons JP, et al. for the Femhrt Study Investigators. Unscheduled bleeding during initiation of continuous combined hormone replacement therapy: a direct comparison of two combinations of norethindrone acetate and ethinyl estradiol to medroxyprogesterone acetate and conjugated equine estrogens. *Menopause.* 2001;8(5).
119. Simon JA, Wysocki S, Brandman J, et al. A comparison of therapy continuation rates of different hormone replacement agents: a 9-month retrospective, longitudinal analysis of pharmacy claims among new users. *Menopause.* 2003;10(1):37-44.
120. Archer DF, Furst K, Tipping D, et al. A randomized comparison of continuous combined transdermal delivery of estradiol-norethindrone acetate and estradiol alone for menopause. *Obstet Gynecol.* 1999;94:498-503.
121. Johnson JV, Davidson M, Archer D, et al. Postmenopausal uterine bleeding profiles with two forms of continuous combined hormone replacement therapy. *Menopause.* 2002;9(1):3.
122. Godsland IF, Gangar K, Walton C, et al. Insulin resistance, secretion, and elimination in postmenopausal women receiving oral or transdermal hormone therapy. *Metabolism.* 1993;42(7):846.
123. Whitcroft SI, Crook D, Marsh MS, et al. Long-term effects of oral and transdermal hormone replacement therapies on serum lipid and lipoprotein concentrations. *Obstet Gynecol.* 1994;84(2):222.
124. Hirvonen E, Lipasti A, Malkonen M, et al. Clinical and lipid metabolic effects of unopposed oestrogen and two oestrogen-progestogen regimens in post-menopausal women. *Maturitas.* 1987;9(1):69.
125. White W, Hanes V, Chauhan V, and Pitt B. Effects of a new hormone therapy, drospirenone and 17-B-Estradiol, in postmenopausal women with hypertension. *Hypertension.* 2006 June;48:1-8.
126. Prestron R, White W, Pitt B, Bakris G, Norris P, and Hanes V. Effects of drospirenone/17-β estradiol on blood pressure and potassium balance in hypertensive postmenopausal women. *Am J Hypertens.* 2005;18:797-804.
127. White W, Pitt B, Preston R, and Hanes V. Antihypertensive effects of drospirenone with 17β-estradiol, a novel hormone treatment in postmenopausal women with stage 1 hypertension. *Circulation.* 2005;112:1979-84.
128. Archer D, Thorneycroft I, Foegh M., Hanes V, Glant M, Bitterman P, and Kempson R. Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. *Menopause.* 2005;12(6):716-27.
129. Schurmann R, Holler T, and Benda N. Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric.* 2004 Jun;7(2):189-96.
130. Lin SQ, Sun LZ, Lin JF, Yang X, Zhang LJ, Qiao J, et al. Estradiol 1 mg and drospirenone 2 mg as hormone replacement therapy in postmenopausal Chinese women. *Climacteric.* 2011;14:472-81.
131. Rowan JP, Simon JA, Speroff L, Ellman H. Effects of low-dose norethindrone acetate plus ethinyl estradiol (0.5 mg/2.5 microg) in women with postmenopausal symptoms: updated analysis of three randomized, controlled trials. *Clin Ther.* 2006 Jun;28(6):921-32.
132. Battaglia C, Cianciosi A, Mancini F, Persico N, Sisti G, Facchinetti F, Busacchi P. Angeliq versus Activelylle in normotensive postmenopausal women: a prospective, randomized pilot study. *Menopause.* 2009 Jul-Aug;16(4): 803-9.

133. Furness S, Roberts H, Marjoribanks J, Lethaby A, Hickey M, Farquhar C. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD000402. DOI: 10.1002/14651858.CD000402.pub3.
134. Canonico M, Plu-Bureau, Lowe GD, Scarabin P. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ*. 2008;336:1227-31.
135. Morch LS, Lokkegaard E, Andreasen AH, Kruger-Kjaer S, Lidegaard O. Hormone therapy and ovarian cancer. *JAMA*. 2009;302(3):298-305.
136. Jaakkola S, Pukkala E, Lyytinen H, Ylikorkala O. Postmenopausal estradiol-progestagen therapy and risk for uterine cervical cancer. *Int J Cancer*. 2012 Aug 15;131(4):E537-E43.
137. Lobo RA, Pinkerton JV, Gass ML, et al. Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. *Fertil Steril* 2009;92:1025–1038.
138. Pickar JH, Yeh I-T, Bachmann G, Speroff L. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/ conjugated estrogens as a menopausal therapy. *Fertil Steril* 2009;92:1018–1024.
139. Archer DF, Lewis V, Carr BR, Olivier S, Pickar JH. Bazedoxifene/ conjugated estrogens (BZA/CE): Incidence of uterine bleeding in postmenopausal women. *Fertil Steril* 2009;92:1039–1044.
140. Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex of bazedoxifene/ conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril* 2009;92:1045–1052.
141. Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: A randomized, controlled trial. *Menopause* 2009;16:1116–1124.
142. Utian W, Yu H, Bobula J, Mirkin S, Olivier S, Pickar JH. Bazedoxifene/conjugated estrogens and quality of life in postmenopausal women. *Maturitas* 2009;63:329–335.
143. Yu H, Racketta J, Chines AA, Mirkin S. Hot flush symptom-free days with bazedoxifene/ conjugated estrogens in postmenopausal women. *Climacteric* 2013;16:252-7.
144. Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH. A randomized, placebo- and active-controlled trial of bazedoxifene/ conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. *Menopause* 2010;17:281–289.
145. Bachmann G, Bobula J, Mirkin S. Effects of bazedoxifene/ conjugated estrogens on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. *Climacteric* 2010;13:132–140.
146. Mirkin S, Komm BS, Pan K, Chines AA. Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women. *Climacteric* 2013;16:338-46.
147. Pinkerton JV, Harvey JA, Pan K, Thompson JR, Ryan KA, Chines AA et al. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. *Obstet Gynecol* 2013;121:959-68.
148. Pinkerton JV, Harvey JA, Lindsay R, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. *J Clin Endocrinol Metab* 2014;99: E189–E198.
149. Pinkerton JV, Abraham L, Psychol C, et al. evaluation of the efficacy and safety of bazedoxifene/ conjugated estrogens for secondary outcomes including vasomotor symptoms in postmenopausal women by years since menopause in the selective estrogens, menopause and response to therapy (SMART) trials. *Journal of Women’s Health* 2014;23(1):18-28.
150. Komm BS, Thompson JR, Mirkin S. Cardiovascular safety of conjugated estrogens plus bazedoxifene: meta-analysis of the SMART trials. *Climacteric*. 2015;18(4):503-11.
151. Doren M, Reuther G, Minne HW, et al. Superior compliance and efficacy of continuous combined oral estrogen-progestogen replacement therapy in postmenopausal women. *Am J Obstet Gynecol*. 1995;173:1446-51.
152. Eiken P, Kolthoff N. Compliance with long-term oral hormonal replacement therapy. *Maturitas*. 1995;22:97-103.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alpha-Glucosidase Inhibitors
AHFS Class 682002
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The alpha-glucosidase inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The antihyperglycemic action of acarbose results from a competitive, reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucosidase hydrolase enzymes. The antihyperglycemic action of miglitol results from a reversible inhibition of membrane-bound intestinal alpha-glucosidase hydrolase enzymes. This enzyme inhibition leads to a delay in glucose absorption and subsequent lowering of postprandial hyperglycemia.¹⁻²

The alpha-glucosidase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. **Acarbose and miglitol are available in a generic formulation.** This class was last reviewed in February 2015.

Table 1. Alpha-Glucosidase Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Acarbose	tablet	Precose®*	acarbose
Miglitol	tablet	Glyset®*	miglitol

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Alpha-Glucosidase Inhibitors

Clinical Guideline	Recommendation(s)
American Diabetes Association: Standards of Medical Care in Diabetes (2016) ³	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) $\geq 6.5\%$, or a fasting plasma glucose (FPG) ≥ 126 mg/dL, or a two-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥ 200 mg/dL). <p>Prevention or delay of type 2 diabetes</p> <ul style="list-style-type: none"> An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥ 150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. Metformin therapy for prevention of type 2 diabetes should be considered in

Clinical Guideline	Recommendation(s)
	<p>those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus.</p> <ul style="list-style-type: none"> • Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p><u>Glycemic goals in adults</u></p> <ul style="list-style-type: none"> • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p><u>Pharmacologic therapy for type 1 diabetes</u></p> <ul style="list-style-type: none"> • Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. • Most patients should use of insulin analogs to reduce hypoglycemia risk. • Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. <p><u>Pharmacologic therapy for type 2 diabetes</u></p> <ul style="list-style-type: none"> • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If the A_{1c} target is not achieved after approximately three months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • Pregestational Diabetes <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1c} <6.5%, to reduce

Clinical Guideline	Recommendation(s)
	<p>the risk of congenital anomalies.</p> <ul style="list-style-type: none"> ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. ● Gestational Diabetes Mellitus <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. ● General Principles for Management of Diabetes in Pregnancy <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. ○ Due to increased red blood cell turnover, A_{1c} is lower in normal pregnancy than in normal nonpregnant women. The A_{1c} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012 and 2015 Update)^{4,5}</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> ● Glycemic targets and glucose-lowering therapies must be individualized. ● Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. ● Unless there are prevalent contraindications, metformin is the optimal first line drug. ● After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. ● Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. ● All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. ● Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> ● It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. ● Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. ● Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin

Clinical Guideline	Recommendation(s)										
	<p>itself in this circumstance.</p> <ul style="list-style-type: none"> • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> • Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. • Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. • In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. • Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. <p>Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations</p> <table border="1"> <thead> <tr> <th data-bbox="500 1749 690 1801">Initial Drug Monotherapy</th> <th data-bbox="690 1749 1408 1801">Metformin</th> </tr> </thead> <tbody> <tr> <td data-bbox="500 1801 690 1833">Efficacy (↓HbA_{1c})</td> <td data-bbox="690 1801 1408 1833">High</td> </tr> <tr> <td data-bbox="500 1833 690 1864">Hypoglycemia</td> <td data-bbox="690 1833 1408 1864">Low risk</td> </tr> <tr> <td data-bbox="500 1864 690 1896">Weight</td> <td data-bbox="690 1864 1408 1896">Neutral/loss</td> </tr> <tr> <td data-bbox="500 1896 690 1906">Side Effects</td> <td data-bbox="690 1896 1408 1906">Gastrointestinal/lactic acidosis</td> </tr> </tbody> </table>	Initial Drug Monotherapy	Metformin	Efficacy (↓HbA _{1c})	High	Hypoglycemia	Low risk	Weight	Neutral/loss	Side Effects	Gastrointestinal/lactic acidosis
Initial Drug Monotherapy	Metformin										
Efficacy (↓HbA _{1c})	High										
Hypoglycemia	Low risk										
Weight	Neutral/loss										
Side Effects	Gastrointestinal/lactic acidosis										

Clinical Guideline	Recommendation(s)						
	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)						
Two Drug Combinations	Metformin + sulfonylurea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)	
Efficacy (↓HbA _{1c})	High	High	Intermediate	Intermediate	High	Highest	
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk	
Weight	Gain	Gain	Neutral	Loss	Loss	Gain	
Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia	
	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)						
Three Drug Combinations	Metformin + sulfonylurea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + SGLT2 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +	
	TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonylurea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonylurea, TZD, SGLT2 inhibitor, or insulin	Sulfonylurea, TZD, DPP-4 inhibitor, or insulin	Sulfonylurea, TZD, or insulin	TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist	
	If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents						
More Complex Insulin Strategies	Combination injectable therapy						
American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012) ⁶	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. 						
American Association of Clinical Endocrinologists/ American College Of Endocrinology: Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015) ⁷	<p>Antihyperglycemic pharmacotherapy for type 2 diabetes</p> <ul style="list-style-type: none"> The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement. Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) 						

Clinical Guideline	Recommendation(s)
	<p>also favorably affect FPG.</p> <ul style="list-style-type: none"> • When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. • The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. • When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists: Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm 2016 (2016)⁸</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} \leq6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • The therapeutic regimen should be as simple as possible to optimize adherence. <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day)

Clinical Guideline	Recommendation(s)
	<p>and life-style modifications will achieve their glycemic goals in a majority of patients.</p> <ul style="list-style-type: none"> • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ Sodium glucose cotransporter 2 (SGLT-2) inhibitors. ○ DPP-4 inhibitors. ○ TZDs (use with caution). ○ Alpha-glucosidase inhibitors. • sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ DPP-4 inhibitors. ○ TZD. ○ Basal insulin. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Three-drug combination therapy</u></p> <ul style="list-style-type: none"> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfoarea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p>Insulin therapy algorithm</p> <ul style="list-style-type: none"> ● Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. ● Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. ● Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. ● Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <p>Basal insulin</p> <ul style="list-style-type: none"> ● Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. ● Titrate insulin dose every two to three days to reach glycemic goals. ● Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. ● Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p>Basal-bolus insulin regimens</p> <ul style="list-style-type: none"> ● Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. ● A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. ● Doses of insulin may be titrated every two to three days to reach glycemic goals. <p>Basal insulin and incretin therapy regimens</p> <ul style="list-style-type: none"> ● Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. ● The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last updated July 2016)⁹</p>	<p>Individualized care</p> <ul style="list-style-type: none"> ● Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop

Clinical Guideline	Recommendation(s)
	<p>any medicines that are not effective.</p> <ul style="list-style-type: none"> • Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p><u>HbA_{1c} targets</u></p> <ul style="list-style-type: none"> • Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. • For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. • In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> ○ reinforce advice about diet, lifestyle and adherence to drug treatment and ○ support the person to aim for an HbA_{1c} level of 7.0% and ○ intensify drug treatment. • Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> ○ who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy ○ for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job ○ for whom intensive management would not be appropriate, for example, people with significant comorbidities. • If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p><u>Drug treatment</u></p> <ul style="list-style-type: none"> • For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost • If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. • Initial drug treatment <ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below

Clinical Guideline	Recommendation(s)
	<p>45 ml/minute/1.73m²;</p> <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². <ul style="list-style-type: none"> ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p>First intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. • Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes. <p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment. • If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. • Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in six months).

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment. • In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p>Insulin-based treatments</p> <ul style="list-style-type: none"> • When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional. • When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. • Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation. ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: <ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals. ○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes: <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch

Clinical Guideline	Recommendation(s)
	<p>to one of the long-acting insulin analogues was made or</p> <ul style="list-style-type: none"> ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. • Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). • Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)¹⁰</p>	<ul style="list-style-type: none"> • Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. • Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes (2012)¹¹</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> • Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. • Match the timing of medication (including insulin) and meals. • Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. • Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals. • Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. • Provide guidance for adjusting medications (insulin) and/or adding carbohydrate

Clinical Guideline	Recommendation(s)
	<p>for physical activity.</p> <p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> • Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. • A lower HbA_{1c} target may be considered if it is easily and safely achieved. • A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> • Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. • Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. • First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. • Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. • Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering medications (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH)

Clinical Guideline	Recommendation(s)
	<p>insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin).</p> <ul style="list-style-type: none"> • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)¹²</p>	<ul style="list-style-type: none"> • Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations ≥ 250 mg/dL. ○ Whose HbA_{1c} is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
<p>National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November 2016)¹³</p>	<p><u>Education and information for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. • Tailor the education programme to each child or young person with type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ life goals. • Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. • Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Encourage children and young people with type 1 diabetes to wear or carry something that identifies them as having type 1 diabetes (e.g., a bracelet). • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. • Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations. • Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p><u>Insulin therapy for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. • Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen. • Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump)

Clinical Guideline	Recommendation(s)
	<p>therapy.</p> <ul style="list-style-type: none"> • Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. • Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. • Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin infusion users. • Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. • Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin (0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%. • Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. • Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. • Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with type 1 diabetes a review of injection sites at each clinic visit. • Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. • If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily injections, continuous subcutaneous insulin infusion [CSII or insulin pump] therapy or once-, twice- or three-times daily mixed insulin injections). <p><u>Oral medicines for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control.

Clinical Guideline	Recommendation(s)
	<p><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. • Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. • Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. • Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain. <p><u>Education and information for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ HbA_{1c} monitoring and targets ○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control ○ the aims of metformin therapy and possible adverse effects ○ the complications of type 2 diabetes and how to prevent them. • Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every 2 years. • Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. <p><u>Dietary management for children and young people with type 2 diabetes</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. • Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. • At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. • Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications. • Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. • Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. • At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI. • Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. • Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy. <p><u>Metformin</u></p> <ul style="list-style-type: none"> • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management (Published 2015; last updated July 2016)¹⁴</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> • Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. • Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target. • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles ○ total glycated hemoglobin estimation (if abnormal hemoglobins). • Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. • Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia. • Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p><u>Self-monitoring of blood glucose</u></p> <ul style="list-style-type: none"> • Advise routine self-monitoring of blood glucose levels for all adults with type 1

Clinical Guideline	Recommendation(s)
	<p>diabetes, and recommend testing at least four times a day, including before each meal and before bed.</p> <ul style="list-style-type: none"> • Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). • Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia. • Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. • Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy) • Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking. <p><u>Continuous glucose monitoring</u></p> <ul style="list-style-type: none"> • Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. • Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause. ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level ≥9%) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in HbA_{1c} of 2.5% or more. • For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. <p><u>Insulin regimens</u></p> <ul style="list-style-type: none"> • Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. • Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin

Clinical Guideline	Recommendation(s)
	<p>regimens (that is, twice-daily mixed, basal only or bolus only).</p> <p><u>Long-acting insulin</u></p> <ul style="list-style-type: none"> • Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. • Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul style="list-style-type: none"> ○ an existing insulin regimen being used by the person that is achieving their agreed targets ○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. • Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p><u>Rapid-acting insulin</u></p> <ul style="list-style-type: none"> • Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. • Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. • If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. <p><u>Mixed insulin</u></p> <ul style="list-style-type: none"> • Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. • Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p><u>Optimizing insulin therapy</u></p> <ul style="list-style-type: none"> • For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously optimized insulin regimen, the following should be considered: <ul style="list-style-type: none"> ○ injection technique ○ injection sites ○ self-monitoring skills ○ knowledge and self-management skills ○ nature of lifestyle ○ psychological and psychosocial difficulties ○ possible organic causes such as gastroparesis. • Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. <p><u>Adjuncts</u></p> <ul style="list-style-type: none"> • Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> • Adults with type 1 diabetes who inject insulin should have access to the insulin

Clinical Guideline	Recommendation(s)
	<p>injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen.</p> <ul style="list-style-type: none"> • Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. • Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. • After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. • Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. • Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. • Check injection site condition at least annually and if new problems with blood glucose control occur.
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)¹⁵</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> • Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. • If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <p><u>Glycemic control goals</u></p> <ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p> <ul style="list-style-type: none"> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the alpha-glucosidase inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Alpha-Glucosidase Inhibitors^{1,2}

Indication(s)	Acarbose	Miglitol
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✓	✓

IV. Pharmacokinetics

The pharmacokinetic parameters of the alpha-glucosidase inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Alpha-Glucosidase Inhibitors¹⁶

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Acarbose	0.5 to 2.0	Negligible (% not reported)	Intestinal wall (extensive, % not reported)	Renal (2), Feces (51)	2
Miglitol	100	<4	Hepatic (% not reported)	Renal (>95)	2

V. Drug Interactions

Major drug interactions with the alpha-glucosidase inhibitors are listed in Table 5.

Table 5. Major Drug Interactions with the Alpha-Glucosidase Inhibitors¹⁶

Generic Name(s)	Interaction	Mechanism
Acarbose	Digoxin	Impaired digoxin absorption is suspected; therefore, serum digoxin concentrations may be reduced, decreasing its therapeutic effects.

VI. Adverse Drug Events

The most common adverse drug events reported with the alpha-glucosidase inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Alpha-Glucosidase Inhibitors^{1,2}

Adverse Events	Acarbose	Miglitol
Dermatologic		
Hypersensitive skin reactions	✓	-
Rash	✓	4.3
Gastrointestinal		
Abdominal pain	19	11.7
Diarrhea	31	28.7
Flatulence	74	41.5
Ileus/subileus	✓	-
Hepatic		
Fulminant hepatitis	-	-
Hepatitis	✓	-
Jaundice	✓	-
Transaminases increased	<4	-
Other		
Edema	✓	-
Low serum iron	-	9.2

✓ Percent not specified.

- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the alpha-glucosidase inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Alpha-Glucosidase Inhibitors^{1,2,17}

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Acarbose	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 25 mg TID with meals; maintenance, 25 to 50 mg TID; maximum, 50 mg TID (≤ 60 kg) or 100 mg TID (> 60 kg)	Safety and effectiveness in pediatric patients have not been established.	Tablet: 25 mg 50 mg 100 mg
Miglitol	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 25 mg TID with meals; maintenance, 50 mg TID; maximum, 100 mg TID	Safety and effectiveness in pediatric patients have not been established.	Tablet: 25 mg 50 mg 100 mg

TID=three times daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the alpha-glucosidase inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Alpha-Glucosidase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Outcomes Trials				
Chiasson et al. ¹⁸ (2003) Acarbose 100 mg TID vs placebo	DB, MC, PC, RCT Patients 40 to 70 years of age, with a BMI 25 to 40 kg/m ² with impaired glucose tolerance test and a FPG 100 to 140 mg/dL	N=1,429 3.3 years (mean duration)	Primary: Number of patients who developed major cardiovascular events Secondary: New cases of hypertension	Primary: Fifteen patients receiving acarbose and 32 patients receiving placebo experienced any cardiovascular event. Acarbose was associated with a 49% RR reduction in the development of any cardiovascular event (HR, 0.51; 95% CI, 0.25 to 0.95; P=0.03) and a 2.5% absolute risk reduction. There was a significant reduction in the risk of MI associated with acarbose treatment; one patient experienced a MI with acarbose and 12 patients with placebo (HR, 0.09; 95% CI, 0.01 to 0.72; P=0.02). Five patients receiving acarbose experienced angina compared to 12 patients receiving placebo (P=0.13). Eleven patients receiving acarbose experienced revascularization procedures and 20 patients receiving placebo (P=0.18). One patient receiving acarbose experienced cardiovascular death compared to two patients receiving placebo (P=0.63). No patient receiving acarbose and two patients receiving placebo experienced congestive heart failure. Two patients receiving acarbose and four patients receiving placebo experienced a cerebrovascular event or stroke (P=0.51). One patient in each group experienced peripheral vascular disease (P=0.93). Secondary: Seventy eight (11%) of the 682 patients receiving acarbose developed hypertension compared to 115 (17%) of the 686 patients receiving placebo. There was a 34% RR decrease in the incidence of new hypertension cases associated with acarbose (HR, 0.66; 95% CI, 0.49 to 0.89; P=0.006) and a 5.3% absolute risk reduction. Reduction in the risk of cardiovascular events (HR, 0.47; 95% CI, 0.24 to 0.90; P=0.02) and hypertension (HR, 0.62; 95% CI, 0.45 to 0.86; P=0.004) associated with acarbose was significant after adjusting for the major risk

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				factors.
Diabetes Prevention Trials				
Chiasson et al. ¹⁹ (2002) Acarbose 100 mg TID vs placebo	DB, MC, PC, RCT Patients 40 to 70 years of age, with a BMI 25 to 40 kg/m ² , and impaired glucose tolerance test according to the WHO criteria, and a FPG 100 to 140 mg/dL	N=1,429 3.3 years (mean duration)	Primary: The development of diabetes on the basis of a yearly oral glucose tolerance test Secondary: Not reported	Primary: One hundred seventeen (17%) patients developed diabetes in the acarbose group compared to 178 (26%) patients in the placebo group (HR, 0.68; 95% CI, 0.54 to 0.85; P=0.0010), resulting in an absolute reduction of 8.7% and a relative reduction of 32.4% when a FPG of 7.0 mmol/L or greater was reported on two consecutive visits as the criterion for the development of diabetes. When any two positive oral glucose tolerance tests with a two-hour plasma glucose of 11.1 mmol/L or greater, 105 (15%) patients converted to diabetes in the acarbose group compared to 165 (24%) patients in the placebo group (HR, 0.64; 95% CI, 0.4981 to 0.8129; P=0.003) for an absolute reduction of 8.7% and a relative reduction of 36.4%. Based on one abnormal plasma glucose concentration, cumulative incidence of diabetes was 221 (32%) patients in the acarbose group and 285 (42%) patients in the placebo group (relative hazard, 0.75; 95% CI, 0.63 to 0.90; P=0.0015). Probability of reverting to normal glucose tolerance over time was significantly higher in patients on acarbose than in those on placebo (P<0.001). Secondary: Not reported
Van de Laar et al. ²⁰ (2006) Acarbose vs placebo, metformin, diet	MA (5 trials) Patients with impaired glucose tolerance or impaired fasting blood glucose	N=2,360 1 to 6 years	Primary: Occurrence of type 2 diabetes Secondary: Cardiovascular morbidity and mortality, glycemic control, lipids, BP, body weight	Primary: In the comparison of acarbose to placebo, the incidence of or conversion to type 2 diabetes was reduced (RR, 0.78; 95% CI, 0.68 to 0.90). Neither acarbose nor metformin had significant effects on the incidence of type 2 diabetes when compared to one another. However, when compared to diet and exercise, acarbose had beneficial effects on the incidence of type 2 diabetes (RR, 0.40; 95% CI, 0.17 to 0.96). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and exercise, or both				<p>There were no significant effects on total mortality or mortality due to cardiovascular causes in trials comparing acarbose to placebo. In one trial (STOP-NIDDM), a decreasing effect on the incidence of cardiovascular disease as a combined end point (MI, angina, revascularization procedures, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease) was reported (RR, 0.47; 95% CI, 0.26 to 0.86).</p> <p>Acarbose decreased PPG by 0.61 mmol/L (95% CI, 0.27 to 0.95) compared to placebo. In the EDIT study, acarbose significantly decreased FPG and PPG in comparison to placebo (P=0.0043 and P=0.0075, respectively). In comparison to metformin, acarbose showed a decreasing effect on PPG (1.40 mmol/L; 95% CI, 0.55 to 2.25). Similarly, acarbose vs diet and exercise also showed significant reductions in FPG and PPG (-1.37 [95% CI, -0.50 to -2.24] and -2.79 mmol/L [95% CI, -1.79 to -3.79]).</p> <p>There were no significant effects on DBP and SBP in trials comparing acarbose to placebo. However, metformin showed significant decreases in both TC and DBP in comparison to acarbose (0.90 mmol/L [95% CI, 0.19 to 1.61] and 6 mm Hg [95% CI, 2.81 to 9.19], respectively).</p> <p>Acarbose decreased body weight by 1.2 kg (95% CI, 0.5 to 1.8) and BMI by 0.3 kg/m² (95% CI, 0.1 to 0.5) compared to placebo.</p>
Type 2 Diabetes – Monotherapy				
<p>Buse et al.²¹ (1998) PROTECT</p> <p>Acarbose 25 to 50 mg TID</p> <p>The dose remained at 50 mg TID, or the dose was increased to 100 mg TID, or a sulfonylurea was</p>	<p>MC, OL, PRO</p> <p>Patients ≥21 years of age with type 2 diabetes who were inadequately controlled with either diet alone or diet and a sulfonylurea</p>	<p>N=6,142</p> <p>28 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline PPG</p>	<p>Primary: Mean HbA_{1c} after 28 weeks was 8.41%. The mean change from baseline in HbA_{1c} at trial end was -0.66% (P<0.001).</p> <p>Secondary: Mean PPG level was 208.1 mg/dL after 28 weeks of therapy. The mean PPG level decreased by 41 mg/dL at trial end (P<0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
added, or the dose of the sulfonylurea was increased.				
Hwu et al. ²² Asian Acarbose Study Group (2003) Acarbose 50 mg TID for 6 weeks, titrated up to 100 mg TID for 12 weeks vs placebo	DB, MC, PC, PG, RCT Asian patients 35 to 70 years of age with type 2 diabetes receiving insulin with inadequate control, an HbA _{1c} 8.0 to 11.0%, requiring ≥2 injections of intermediate insulin per day, and a BMI ≤35 kg/m ²	N=117 18 weeks	Primary: Change in baseline HbA _{1c} Secondary: Changes in baseline FPG, PPG, and lipids	Primary: HbA _{1c} improved with acarbose (-0.5±1.3%) and worsened with placebo (0.2±1.2%). The comparison between the two treatments showed a difference of -0.69% (95% CI, -1.18 to -0.20; P=0.008) in favor of acarbose. Secondary: FPG decreased with acarbose by trial end, but there was not a significant difference between placebo (0.04 mmol/L; 95% CI, -1.28 to 1.66; P=0.094). Differences between the two treatments were significant for the PPG data (-1.89 mmol/L; 95% CI, -3.50 to -0.28; P=0.029), but was not significant for the two-hour post-prandial data (-1.83 mmol/L; 95% CI, -3.67 to 0.00; P=0.051). There were no differences between the two treatments, from baseline to trial end, for TG, TC, and LDL-C (P=0.378, P=0.935, P=0.294, respectively). There was a small decrease in HDL-C with acarbose (P=0.049).
Josse et al. ²³ (2003) Acarbose 50 to 100 mg TID vs placebo	DB, PC, RCT Patients >65 years of age with type 2 diabetes treated with diet alone	N=192 1 year	Primary: Change in HbA _{1c} , FPG, fasting insulin, relative insulin sensitivity, and glucose; insulin incremental AUC Secondary: Not reported	Primary: Differences in the change from baseline in HbA _{1c} between acarbose and placebo was -0.6% (P<0.05). Acarbose 100 mg TID resulted in a greater HbA _{1c} treatment effect compared to acarbose 50 TID (-0.9 vs -0.2%; P value not reported). Change in FPG level was greater with acarbose compared to placebo (-0.7 mmol/L; P<0.05). Change in fasting insulin was -9±4 and -9 pmol/L with acarbose and placebo; the difference was not significant (P value not reported). Acarbose showed a significant reduction in glucose and insulin incremental AUC compared to placebo (glucose, -2.1 mmol/h l [P<0.05])

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>and insulin, -45 pmol/h l; [P<0.05]).</p> <p>Acarbose showed a significant reduction in relative insulin resistance compared to placebo (-0.8; P<0.05).</p> <p>Secondary: Not reported</p>
<p>Lam et al.²⁴ (1998)</p> <p>Acarbose 50 mg TID for 4 weeks, titrated up to 100 mg TID for 20 weeks</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, RCT</p> <p>Patients with type 2 diabetes, BMI <30 kg/m², HbA_{1c} 8.4 to 10.8%, and on maximal doses of glibenclamide* or gliclazide† and metformin for ≥6 months</p>	<p>N=90</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, PPG, insulin levels, and fasting lipid levels</p> <p>Secondary: Not reported</p>	<p>Primary: Acarbose was associated with greater reductions in HbA_{1c} (-0.5±0.2 vs 0.1±0.2%; P=0.038), one-hour PPG (-2.3 ±0.4 vs 0.7±0.4 mmol/L; P<0.001) and body weight (-0.54±0.32 vs 0.42±0.29 kg; P<0.05).</p> <p>No significant differences between the two treatments with regards to FPG, lipids, or fasting and postprandial insulin levels (P values not reported).</p> <p>Gastrointestinal symptoms were the most common side effects with flatulence occurring the most compared to placebo (P<0.05).</p> <p>Secondary: Not reported</p>
<p>Lin et al.²⁵ (2003)</p> <p>Acarbose 100 mg TID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Asian patients 35 to 70 years of age with type 2 diabetes for ≥3 months, HbA_{1c} 7.0 to 10.0%, stable body weight (≤35 kg), and uncontrolled by diet and sulfonylureas</p>	<p>N=69</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline blood glucose (FPG and PPG), serum insulin (fasting and one-hour postprandial), urinary glucose, safety</p>	<p>Primary: Acarbose was associated with significantly greater reductions in HbA_{1c} (-0.91 vs 0.13%; P=0.0018) and PPG levels (-2.84 vs 0.28 mmol/L; P=0.002).</p> <p>Secondary: There were no significant differences between the treatment groups regarding changes in FPG (P=0.1941), fasting insulin (P=0.5003), insulin PPG (P=0.2799), urinary glucose (P value not reported), and body weight (P value not reported).</p> <p>Change in blood glucose (FPG and PPG) was significant for acarbose compared to placebo (P=0.0020).</p> <p>Adverse events occurred with similar frequency with both treatments except for drug-related gastrointestinal side effects with acarbose (48.5 vs</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Mori et al.²⁶ (2011)</p> <p>Acarbose 300 mg/day, administered on 2 of 4 days</p> <p>vs</p> <p>no treatment</p>	<p>SA</p> <p>Adults with type 2 diabetes</p>	<p>N=10</p> <p>4 days</p>	<p>Primary: Glucose fluctuations</p> <p>Secondary: Not reported</p>	<p>12.5%; P value not reported).</p> <p>Primary: During treatment, significant decreases in median of 24-hour mean blood glucose (22.48 vs 32.78 mg/dL; P=0.004), 24-hour mean blood glucose fluctuations (453.27 vs 677.05 mg/dL; P=0.002), and mean amplitude of glycemic excursions (65.00 vs 97.09; P=0.010) were achieved with acarbose compared to no treatment.</p> <p>Secondary: Not reported</p>
<p>Jian-bin et al.²⁷ (2011)</p> <p>Acarbose 50 mg TID</p> <p>vs</p> <p>no treatment</p> <p>All patients received existing insulin regimens.</p> <p>After an initial 3 day continuous glucose monitoring test, patients with mean amplitude of glycemic excursions >3.4 mmol/L received acarbose for 2 weeks (high group); patients</p>	<p>PRO</p> <p>Type 2 diabetics receiving premixed insulin BID for >3 consecutive months and HbA_{1c} <6.5%</p>	<p>N=106 (includes 20 control subjects who had normal glucose regulation)</p> <p>3 days</p>	<p>Primary: Glycemic variability, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: Among the 86 patients, the mean amplitude of glycemic excursions and mean of daily differences of type 2 diabetes groups were all higher compared to control patients (P<0.01).</p> <p>Twenty-four percent of patients in the high group (n=11) had a total of 13 hypoglycemic events, and 10 of the 13 events occurred at night. Five percent of patients in the low group (n=2) had a total of two hypoglycemic events, and both occurred at night (24 vs 5%; P<0.01). Mean amplitude of glycemic excursion value was correlated with hypoglycemia value and two-hour PPG value (P<0.05).</p> <p>After further treatment with acarbose and second continuous glucose monitoring, mean amplitude of glycemic excursions and mean of daily differences values in the high group were all significantly decreased (40%; P<0.01, and 15%; P<0.05, respectively), but remained higher compared to control patients (P<0.05). Two percent of patients (n=1) had a total of one hypoglycemic event.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with values <3.4 mmol/L did not receive additional treatment (low group).				
<p>Feinbock et al.²⁸ (2003)</p> <p>Acarbose 50 to 200 mg TID</p> <p>vs</p> <p>glimepiride 1 to 6 mg QD</p>	<p>MC, OL, PG, RCT</p> <p>Patients from 36 to 80 years of age with type 2 diabetes uncontrolled on diet alone, with an HbA_{1c} ≥7.8%, and BMI 24 to 35 kg/m²</p>	<p>N=219</p> <p>20 weeks</p>	<p>Primary: Number of responders in each group (defined as a FPG ≤7.8 mmol/L at the final visit)</p> <p>Secondary: Changes in HbA_{1c}, weight, PPG, and C-peptide levels from baseline</p>	<p>Primary: Glimepiride treatment was associated with a significant responder rate compared to acarbose, 61 vs 34% respectively (P<0.001).</p> <p>Glimepiride resulted in significant decreases in HbA_{1c} (2.5±2.2%) as compared to acarbose (1.8±2.2%; P=0.014).</p> <p>Secondary: FPG levels were significantly decreased with glimepiride as compared to acarbose (2.6±2.6 vs 1.4±2.8 mmol/L; P=0.004).</p> <p>There was a greater reduction in HbA_{1c} in the glimepiride group (2.5±2.2%) compared to the acarbose group (1.8±2.2%; P=0.014).</p> <p>Decreased glucose response to breakfast was significant for glimepiride compared to acarbose (P=0.0001).</p> <p>Weight loss was observed in the acarbose group (P=0.001) and glimepiride group (P=0.8) from baseline.</p> <p>C-peptide levels were higher in the glimepiride group compared to the acarbose group at study end point (5.44±2.26 vs 4.57±1.93 ng/mL; P=0.0004; intra-individual difference, 0.53 ±1.7 vs -0.31 ±1.72 ng/mL; P=0.002).</p>
<p>Zhou et al.²⁹ (2013)</p> <p>Acarbose 50 mg TID</p> <p>nateglinide 120 mg TID</p>	<p>AC, ML, OL, PG, RCT</p> <p>Patients 18 to 75 years who were antihyperglycemic agent-naïve with type 2 diabetes</p>	<p>N=103</p> <p>2 weeks</p>	<p>Primary: Incremental area under the curve of postprandial blood glucose (AUC_{pp}) during continuous glucose monitoring (CGM)</p>	<p>Primary: Both treatment groups showed a significant decrease in the AUC_{pp} of treatment (vs baseline, P<0.001), but the decrease achieved by the two therapies was not significantly different (nateglinide vs acarbose, P=0.691).</p> <p>Secondary: No significant differences between treatment groups occurred for</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	(HbA _{1c} 6.5 to 9.0%)		Secondary: Additional CGM measures, serum glycated albumin, safety	secondary efficacy outcomes, except for therapy-mediated effects on insulin levels. The insulin concentrations in the nateglinide group increased at 30 minutes (P<0.0001) and at 120 minutes (P=0.0012), with statistical differences between pretreatment and posttreatment. In contrast, compared with baseline, the insulin concentrations at the end point in the acarbose group decreased at 30 minutes and at 120 minutes with statistical differences between pretreatment and post-treatment (both P<0.0001). Both treatments were well-tolerated.
van de Laar et al. ³⁰ (2004) Acarbose titrated to 100 mg TID vs tolbutamide titrated 2,000 mg daily in 3 divided doses	DB, RCT Newly diagnosed patients with type 2 diabetes between 40 to 70 years of age and a FPG level between 6.7 and 20.0 mmol/L after an 8-week dietary treatment period	N=96 30 weeks	Primary: Change in HbA _{1c} from baseline Secondary: Change in fasting and postload blood glucose and insulin levels, plasma lipids, tolerability	Primary: Both treatment groups showed a decrease in HbA _{1c} . The HbA _{1c} change from baseline for the acarbose group was -1.1 vs -1.8% for the tolbutamide group. The difference between the groups was 0.6% in favor of tolbutamide (90% CI, 0.3 to 0.9 and 95% CI, 0.2 to 1.0). Secondary: Difference in mean decrease of FPG was 1.0 mmol/L in favor of tolbutamide (95% CI, 0.3 to 1.7). No significant differences were seen in postload blood glucose, fasting and postload insulin levels, or lipids.
Wagner et al. ³¹ (2006) Acarbose 100 mg TID vs aerobic/anaerobic exercise group training for 50 minutes 3 times weekly vs	RCT Patients 45 to 60 years of age with type 2 diabetes for ≥3 months, HbA _{1c} <7.5%, and BMI 25 to 30 kg/m ²	N=62 12 weeks	Primary: Change in baseline HbA _{1c} , insulin sensitivity (M value), regional fat distribution, V _{O₂max} (a measure of physical fitness) Secondary: Not reported	Primary: At trial end, acarbose resulted in no effects on HbA _{1c} , FPG, M value, BMI, body composition, or V _{O₂max} . However, fasting plasma proinsulin level was significantly reduced (P=0.009). With exercise there were significant reductions in BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat area. Although V _{O₂max} was unchanged, there was an increase in maximal workload (P=0.005) and in the M value (P=0.017). HbA _{1c} was unchanged. Acarbose plus exercise resulted in significant decreases in BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat. Maximal workload, V _{O₂max} , and M values were all increased (P=0.028, P=0.046, and P=0.002, respectively). Additionally, fasting plasma proinsulin levels were significantly reduced (P=0.013), as well as HbA _{1c}

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acarbose 100 mg TID plus exercise				(P value not reported). Secondary: Not reported
de Luis Roman et al (abstract). ³² (2004) Miglitol 50 mg BID for 1 week, followed by 50 mg TID	OL Patients with type 2 diabetes inadequately controlled (HbA _{1c} >7.5%) on sulfonylureas and insulin	N=33 3 months	Primary: Change in weight, height, BMI, SBP, DBP, HbA _{1c} , number of episodes of peripheral hypoglycemia, basal glucose, albuminuria, TC, LDL-C, HDL-C, TG, and transaminases Secondary: Not reported	Primary: Blood glucose and HbA _{1c} decreased 4.8 and 5.8%, respectively. There was a decrease in the number of hypoglycemia episodes (39.4% previous quarter vs 3% during the miglitol quarter). The required dose of sulfonylureas decreased (86.2±24.3 vs 64.6 ±21.9 mg/day; P<0.05). TC, HDL-C, and LDL-C were not modified. There was a reduction in TG from 145.2 ±111.0 to 133.1±79.0 mg/dL (P<0.05). Fifteen percent of patients experienced digestive discomfort, which disappeared two or three weeks after beginning the treatment. Secondary: Not reported
Aoki et al. ³³ (2007) Miglitol, administered prior to breakfast vs miglitol, administered 15 minutes after the start of breakfast vs	XO Adult patients with type 2 diabetes, BMI 26.7 kg/m ² (mean), HbA _{1c} 9.3% (mean), and an average duration of diabetes of 7.4 years	N=13 180 minutes	Primary: Effect of plasma glucose at 0, 30, 60, 120, and 180 minutes after breakfast; effect on serum insulin Secondary: Not reported	Primary: At 30 and 60 minutes, plasma glucose levels were significantly decreased in those who took miglitol just before breakfast compared to control (P<0.05). At 60 and 120 minutes, plasma glucose levels were significantly decreased in those taking miglitol 15 minutes after breakfast (P<0.05) while those taking miglitol 30 minutes after breakfast had significant reductions at 120 and 180 minutes (P<0.05) compared to control. There were no significant differences between groups. The AUC of serum insulin was lower with all three groups compared to control. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
miglitol, administered 30 minutes after the start of breakfast vs placebo				Not reported
Johnston et al. ³⁴ (1998) Miglitol 25 to 50 mg TID vs glyburide 1.25 to 20 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥60 years of age with type 2 diabetes treated with diet alone for ≥12 weeks, HbA _{1c} 6.5 to 10.0%, and FPG >140 mg/dL	N=411 1 year	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline plasma glucose, serum insulin, and TG	Primary: Mean placebo-subtracted HbA _{1c} reduction from baseline was -0.50% with miglitol 25 mg TID (P<0.05 vs glyburide), -0.41% with miglitol 50 mg TID (P<0.05 vs glyburide), -0.93% for glyburide QD, and -0.01% for placebo (P<0.05 vs all active treatments). Secondary: Changes in mean plasma glucose (AUC) were +716 mg·min/dL with placebo (P<0.05 vs all active treatments), -3,361 mg·min/dL with miglitol 25 mg TID, -5,462 mg·min/dL with miglitol 50 mg TID, and -3,615 mg·min/dL with glyburide (P=0.0001 for miglitol 50 mg TID vs placebo). Postprandial insulin levels were significantly greater with glyburide compared to placebo and miglitol (P<0.01). Mean changes from baseline to end point for fasting TG were 1.01 with placebo and miglitol 25 mg TID, 0.98 with miglitol 50 mg TID, and one with glyburide (P=0.573 for miglitol 50 mg vs placebo). Mean changes from baseline to end point for TG (AUC) were 1.01 with placebo, 1.03 with miglitol 25 mg TID, 1.00 with miglitol 50 mg TID, and 1.06 with glyburide (P=0.8559 miglitol 50 mg TID vs placebo). Hypoglycemia, weight gain, and routine and serious cardiovascular events were more frequent in the glyburide group (P<0.05 vs placebo and miglitol).
Tsujino et al. ³⁵ Acarbose 50 mg,	RCT, XO Patients 20 to 79	N=10 4 days	Primary: Glucose variability	Primary: No significant differences in regard to the range of increase in glucose levels from baseline to peak, time to peak PPG levels from the preprandial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>administered before each meal on day 2</p> <p>vs</p> <p>miglitol 100 mg, administered before each meal on day 2</p> <p>Alternative treatments were administered on day 3 in a XO design.</p>	<p>years of age with type 2 diabetes, taking α-glucosidase inhibitors without any other antidiabetic medications</p>		<p>Secondary: Not reported</p>	<p>period, and AUC for glycemic variability from the preprandial period to three hours after each meal between the two treatments were observed. The range of increase in glucose levels at 30 minutes (0.4 vs 30.7 mg/dL; $P<0.0001$) and 60 minutes (32.8 vs 67.5 mg/dL; $P<0.0001$) after lunch and 30, 60, and 90 minutes after dinner (3.3 vs 22.2 mg/dL; $P=0.0249$, 36.6 vs 67.5 mg/dL; $P<0.0001$, and 60.5 vs 81.6 mg/day; $P=0.0073$, respectively) were significantly smaller with miglitol compared to acarbose.</p> <p>Secondary: Not reported</p>
<p>van de Laar et al.³⁶ (2005)</p> <p>α-glucosidase inhibitor monotherapy</p>	<p>MA (41 trials)</p> <p>Patients with type 2 diabetes who received no other antidiabetic medication</p>	<p>N=8,130</p> <p>≥ 12 weeks</p>	<p>Primary: Mortality, morbidity, quality of life, glycemic control, insulin, or C-peptide levels, lipids, body weight, safety</p> <p>Secondary: Not reported</p>	<p>Primary: There was only limited data on mortality, morbidity, and quality of life. Three trials reported mortality outcomes and found no differences between treatments.</p> <p>Acarbose demonstrated an effect on glycemic control compared to placebo: HbA_{1c}, -0.8% (95% CI, -0.9 to -0.7); FPG, -2.3 mmol/L (95% CI, -2.7 to -1.9); and post-load glucose, -2.3 mmol/L (95% CI, -2.7 to -1.9). The effect on HbA_{1c} from acarbose 50 to 300 mg TID was not dose-dependent. There seemed to be a dose dependency with miglitol in regards to HbA_{1c}: miglitol 25, 50, 100, and 200 mg TID decreased HbA_{1c} by 0.46, 0.58, 0.79, and 1.26%, respectively.</p> <p>A decreasing effect on post-load insulin was found.</p> <p>There were no clinically relevant effects on lipids or body weight found.</p> <p>Adverse events were generally of gastrointestinal origin and dose dependent.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
<p>Bolen et al.³⁷ (2007)</p> <p>Biguanides</p> <p>vs</p> <p>meglitinides</p> <p>vs</p> <p>TZDs</p> <p>vs</p> <p>α-glucosidase inhibitors</p> <p>vs</p> <p>second-generation sulfonylureas</p>	<p>MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs)</p> <p>Patients with type 2 diabetes</p>	<p>N=136 (articles on intermediate outcomes)</p> <p>N=167 (articles on adverse events)</p> <p>N=68 (articles on microvascular outcomes and mortality)</p> <p>Duration varied</p>	<p>Primary: Intermediate outcomes: HbA_{1c}, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes</p> <p>Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events</p>	<p>Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA_{1c} level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.</p> <p>TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C.</p> <p>TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP.</p> <p>Most agents except metformin increased body weight by 1 to 5 kg.</p> <p>In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; $P<0.05$).</p> <p>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).</p> <p>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.</p> <p>Secondary: According to several RCTs and some OS trials, sulfonylureas and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).</p> <p>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.</p> <p>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.</p> <p>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.</p>
<p>Saenz et al.³⁸ (2005)</p> <p>Metformin monotherapy</p> <p>vs</p> <p>placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin</p>	<p>MA (29 RCTs)</p> <p>Adult patients with type 2 diabetes</p>	<p>N=5,259</p> <p>≥ 3 months</p>	<p>Primary:</p> <p>Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from</p>	<p>Primary:</p> <p>Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes ($P=0.009$) and for all-cause mortality ($P=0.03$).</p> <p>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes ($P=0.004$), diabetes-related death ($P=0.03$), all cause mortality ($P=0.01$), and MI ($P=0.02$).</p> <p>Secondary:</p> <p>Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>MI, stroke, peripheral vascular disease, renal disease, hypoglycemia or hyperglycemia, and sudden death); all-cause mortality</p> <p>Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, microalbuminuria, glomerular filtration rate, renal plasma flow</p>	
<p>Richter et al.³⁹ (2006)</p> <p>Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials)</p> <p>or</p> <p>pioglitazone</p>	<p>MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG</p> <p>Adults with type 2 diabetes, trial duration of at least 24 weeks</p>	<p>22 trials</p> <p>N=6,200 randomized to pioglitazone treatment (total N not reported)</p> <p>24 weeks to 34.5 months</p>	<p>Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects</p> <p>Secondary: Health-related quality of life and HbA_{1c}</p>	<p>Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095).</p> <p>Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone)</p> <p>Some studies had more than one treatment arm.</p>				<p>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and -0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 kg/m². Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled.</p> <p>Secondary: No study investigated health-related quality of life.</p> <p>Active glucose-lowering compounds like metformin, glibenclamide‡, gliclazide* or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (P values not reported).</p>
<p>Monami et al.⁴⁰ (2008)</p> <p>Metformin</p> <p>vs</p> <p>sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists</p>	<p>MA</p> <p>Patients with type 2 diabetes mellitus</p>	<p>N=7,890 (27 RCT)</p> <p>Variable duration</p>	<p>Primary: Reduction in HbA_{1c} at 16 to 36 months</p> <p>Secondary: Not reported</p>	<p>Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94), -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.</p> <p>In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.</p> <p>Secondary: Not reported</p>
Type 2 Diabetes – Combination Therapy				
<p>Zhang et al.⁴¹ (2013)</p>	<p>MC, OS, PRO</p> <p>Patients aged ≥18</p>	<p>N=15,034 (efficacy); 15,661</p>	<p>Primary: Efficacy (2-hour PPG, HbA_{1c} and</p>	<p>Primary: Mean 2-hour PPG was reduced from 241.8 mg/dL at the initial visit to 170.2 mg/dL at the final visit. Mean HbA_{1c} decreased from 8.2% at the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
36.8% of patients received acarbose (25 to 600 mg/day) as monotherapy; 63.2% of patients received combination therapy, with acarbose being administered with one (37.5%), two (20.3%) or more (5.4%) anti-diabetic medications	years and had untreated or pre-treated type 2 diabetes or an indication for acarbose treatment and no acarbose treatment within the 3 months before study inclusion	(safety) 3 months	FBG at initial visit when acarbose was prescribed vs up to 3 months later), safety (adverse events) Secondary: Not reported	initial visit to 7.2% at the final visit. FBG decreased from 157.4 mg/dL at the initial visit to 124.8 mg/dL at the final follow-up visit. The most common adverse events and drug-related adverse events were gastrointestinal disorders, mainly flatulence, abdominal distension, and diarrhoea. No other type of adverse event occurred in more than 0.5% of patients. Efficacy was rated as 'good' or 'very good' by 85.8% of physicians, 'sufficient' by 12.1%, and 'insufficient' by 2.1% of physicians (data were missing for 57 patients). The overall tolerability of acarbose was rated by physicians as 'very good' or 'good' by 85.7% of physicians, 'sufficient' by 13.5%, and 'insufficient' by 0.9% of physicians (data were missing for 144 patients). Overall, 95.7% of physicians and 95.3% of patients were 'very satisfied' or 'satisfied' with treatment.
Halimi et al. ⁴² (2000) Acarbose 50 to 100 mg TID and metformin 850 mg BID to TID vs metformin 850 mg BID to TID and placebo	DB, PC, PG, RCT Patients 30 to 70 years of age with type 2 diabetes, BMI 25 to 35 kg/m ² , having poor glycemic control despite receiving metformin ≥2 months before the study start	N=152 6 months	Primary: HbA _{1c} at trial end Secondary: Blood glucose, insulin profiles, TG	Primary: Mean difference in HbA _{1c} from baseline to trial end was -0.7±1.2% with acarbose compared to 0.2±1.3% with placebo (P=0.0001). Patients were classified as responders if their HbA _{1c} values at trial end were <7.0% or had decreased by <15% relative to baseline. The total numbers of responders were 25 of 49 (42%) patients receiving acarbose and 12 of 70 (17%) patients receiving placebo (P=0.002). Secondary: Mean difference in the fasting blood glucose level from baseline to trial end was -1.0±2.8 mmol/L with acarbose compared to 1.3±2.8 mmol/L with placebo (P=0.0001). Mean difference in two-hour PPG level from baseline to trial end was -1.4±3.8 mmol/L with acarbose compared to 1.1±3.5 mmol/L with placebo (P=0.0001). Mean changes between acarbose compared to placebo for TG, fasting and postprandial serum insulin were not significant (P value not significant).
Phillips et al. ⁴³ (2003)	DB, MC, PC, PG, RCT	N=83	Primary: Change in baseline	Primary: Mean HbA _{1c} increased with placebo from 7.82±0.83% at baseline to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Acarbose 50 mg to 100 mg BID and metformin (existing therapy)</p> <p>vs</p> <p>metformin (existing therapy) and placebo</p>	<p>Patients \geq40 years of age with type 2 diabetes for \geq6 months, BMI 25 to 35 kg/m², HbA_{1c} 7.0 to 10.0% at screening week and 6.8 to 10.2% at baseline, and inadequately controlled by metformin</p>	<p>24 weeks</p>	<p>HbA_{1c}</p> <p>Secondary: Change in baseline FPG</p>	<p>8.10\pm1.06% at week 12 and 8.50\pm1.44% at trial end. The mean increase after 24 weeks was 0.68\pm1.17%, with a significant overall time effect (P=0.0001).</p> <p>With acarbose, mean HbA_{1c} decreased from 8.02\pm0.85% at baseline to 7.78\pm1.00% at week 12 (P=0.0261). At the trial end, mean HbA_{1c} increased to 7.97\pm1.10%. There was no significant overall time effect for acarbose (P value not reported).</p> <p>Adjusted least square means for the change in HbA_{1c} from baseline to trial end showed a decrease of 0.16\pm0.18% with acarbose compared to an increase of 0.86\pm0.16% with placebo. There was a significant difference between the treatment groups of 1.02% (95% CI, 0.543 to 1.497; P=0.0001).</p> <p>Secondary: Mean FPG levels increased with placebo from baseline (9.41\pm1.99 mmol/L) to week four (10.06\pm2.43 mmol/L) to trial end (10.77\pm3.39 mmol/L). The levels only changed slightly with acarbose.</p> <p>Mean FPG increases were 1.36\pm2.88 mmol/L with placebo and 0.08\pm1.98 mmol/L with acarbose. The adjusted least square means showed increase at trial end with both treatments of 0.34\pm0.42 mmol/L with acarbose vs 1.48\pm0.39 mmol/L with placebo, with a significance of 1.132 mmol/L between the two treatments (95% CI, 0.056 to 2.208; P=0.0395).</p>
<p>Bayraktar et al.⁴⁴ (1996)</p> <p>Acarbose 50 to 100 mg TID and a sulfonylurea</p> <p>vs</p> <p>metformin 500 mg TID and a sulfonylurea</p>	<p>RCT, XO</p> <p>Patients from 30 to 63 years of age with type 2 diabetes for 2 to 20 years, HbA_{1c} >8.5%, FPG>7.7 mmol/L, or a PPG>10 mmol/L on maximum doses of gliclazide† (240 mg daily)</p>	<p>N=18</p> <p>20 weeks</p>	<p>Primary: Changes in FPG, PPG, HbA_{1c}, TG, cholesterol, fibrinogen, insulin levels, and C-peptide levels from baseline</p> <p>Secondary: Not reported</p>	<p>Primary: Mean FPG, PPG, and HbA_{1c} decreased at the end of each combination treatment period as compared with baseline levels (P<0.05).</p> <p>PPG level in the acarbose group was lower than the level achieved by the group using metformin (P<0.05).</p> <p>There was a significant decrease between pre- and posttreatment 2-hour PPG levels in each group (-5.3\pm0.4 for acarbose vs -2.9\pm0.3 for metformin; P<0.05).</p> <p>There were small reductions in fibrinogen, insulin, and C-peptide levels in</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>each group, but the differences were not statistically significant.</p> <p>Secondary: Not reported</p>
<p>Bao et al.⁴⁵ (2010)</p> <p>Glipizide XL</p> <p>vs</p> <p>glipizide XL plus acarbose</p>	<p>AC, OL, RCT</p> <p>Newly diagnosed type 2 diabetics, 30 to 70 years of age, with HbA_{1c} 7.0 to 9.8%, and no prior use of antidiabetic medications</p>	<p>N=40</p> <p>8 weeks</p>	<p>Primary: Glycemic control, improvements in insulin secretion and sensitivity, glycemic variability, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: After eight weeks, FPG, two-hour post-oral glucose tolerance test plasma glucose, mean blood glucose, HbA_{1c}, glycated albumin, and HOMA-IR were significantly decreased with both treatments. HOMA-B increased significantly compared to baseline (P<0.01 for both). Compared to glipizide XL, combination therapy had significantly lower mean blood glucose and HOMA-IR values after eight weeks (P<0.05 for both). Mean changes in mean blood glucose, HbA_{1c}, and glycated albumin were all greater with combination therapy compared to monotherapy, with only differences in mean blood glucose reaching significant. The overall glucose-lowering and -stabilizing effects were more pronounced with combination therapy.</p> <p>Over the duration of the trial, the decreases in mean amplitude of glycemic excursions and AUC_{postprandial incremental} were significant with both treatments (P<0.01). There was also a significant decrease in mean of daily differences with combination therapy compared to baseline (P<0.01). Patients receiving combination therapy had significantly lower mean of daily differences, mean amplitude of glycemic outcomes, and AUC_{postprandial incremental} values compared to patients receiving monotherapy after eight weeks (P<0.05 for all).</p> <p>There were no significant between-group differences in either the frequency or the duration of hypoglycemia. The mean duration of hypoglycemia was 88.8±84.7 minute per event with monotherapy and 176.3±123.5 minute per event with combination therapy (P=0.114). Patients receiving monotherapy had 0.7±0.4 events per day compared to 0.8±0.4 events per day in patients receiving combination therapy (P=0.612). There was no difference in total instances of severe hypoglycemia reported.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Lopez-Alvarenga et al.⁴⁶ (1999)</p> <p>Acarbose 100 mg TID, chlorpropamide 500 mg daily, and metformin 1,200 mg daily</p> <p>vs</p> <p>NPH insulin at bedtime, chlorpropamide 500 mg daily, and metformin 1,200 mg daily</p> <p>vs</p> <p>chlorpropamide (500 mg daily), metformin (1,200 mg daily), and placebo</p>	<p>DB, RCT, XO</p> <p>Patients with type 2 diabetes from 35 to 70 years of age with BMI 23 to 35 kg/m², with a FPG >8.8 mmol/L despite maximal doses of chlorpropamide and metformin for at least 2 months</p>	<p>N=46</p> <p>42 weeks</p>	<p>Primary: Change in FPG from baseline, body weight, HbA_{1c}, fasting insulin, fasting C-peptide, intravenous glucose tolerance test (incremental area), glucose meal tests (incremental area)</p> <p>Secondary: Not reported</p>	<p>Primary: Changes in FPG from baseline were not significant for placebo (P=0.62), but were significant for acarbose (P=0.05) and insulin (P=0.003).</p> <p>Changes in HbA_{1c} from baseline were not significant for placebo (P=0.62) and acarbose (P=0.3), but were significant for insulin (P=0.008).</p> <p>Changes in body weight were not significant in any group (P=0.2 vs baseline).</p> <p>Changes in fasting insulin from baseline were not significant for placebo (P=0.38), but were significant for acarbose (P=0.03) and insulin (P=0.02).</p> <p>Changes in fasting C-peptide from baseline were not significant in any group, placebo (P=0.7), acarbose (P=0.5), and insulin (P=0.24).</p> <p>Changes in intravenous glucose tolerance test (incremental area) from baseline were not significant in any group, placebo (P=0.36), acarbose (P=0.91), and insulin (P=0.94).</p> <p>Changes in glucose meal tests (incremental area) from baseline were not significant for placebo (P=0.84) and insulin (P=0.08), but were for acarbose (P=0.02).</p> <p>Changes in insulin (incremental area) from baseline were not significant for any group, placebo (P=0.92), acarbose (P=0.3), and insulin (P=0.43).</p> <p>Thirty-seven percent of patients developed severe bloating during acarbose use. This was significant (P<0.05) compared to acarbose and placebo or insulin.</p> <p>Secondary: Not reported</p>
<p>Nemoto et al.⁴⁷ (2011)</p> <p>Miglitol 50 mg</p>	<p>DB, PC, RCT</p> <p>Patients ≥20 years of age with type 2</p>	<p>N=107</p> <p>12 weeks (plus an</p>	<p>Primary: Change in baseline PPG and HbA_{1c}</p>	<p>Primary: The mean decrease in PPG with miglitol was significantly larger compared to placebo (-60.3±70.1 vs 5.1±68.2 mg/dL; P<0.001). The decrease in plasma glucose AUC was significantly larger with miglitol</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>TID vs placebo</p> <p>All patients received existing insulin regimens.</p>	<p>diabetes receiving insulin therapy, plasma glucose level at either 1 or 2 hours after a meal was ≥ 180 mg/dL, and HbA_{1c} $\geq 6.5\%$</p>	<p>additional 4 to 10 week observation period)</p>	<p>Secondary: Safety</p>	<p>compared to placebo (-102.8 ± 122.2 vs 8.7 ± 121.1 mg/dL; $P < 0.001$).</p> <p>Miglitol exhibited a significantly lower HbA_{1c} compared to placebo from week eight to trial end. The decrease from baseline in HbA_{1c} at week 12 was significantly greater with miglitol compared to placebo (-0.37 ± 0.68 vs $0.04 \pm 0.56\%$; $P < 0.001$).</p> <p>Secondary: The total incidence of adverse events was 78.5 and 76.0% with miglitol and placebo. Adverse events with high incidence included flatulence (20.6 vs 12.0%), abdominal distension (15.0 vs 4.0%), diarrhea (14.0 vs 4.0%), and hypoglycemia (39.3 vs 35.0%). The incidences of abdominal distention and diarrhea were significantly higher with miglitol ($P < 0.05$ for both). All hypoglycemic events were mild and improved without treatment, by ingestion of glucose, supplements, or meals.</p>
<p>Hsieh et al.⁴⁸ (2011)</p> <p>Miglitol 50 mg TID, titrated up to 100 mg TID vs placebo</p> <p>Patients received existing sulfonylurea regimens.</p>	<p>DB, MC, PC, RCT</p> <p>Chinese patients >20 years of age with type 2 diabetes, FPG 100 to 240 mg/dL, HbA_{1c} 6.5 to 10.0%, history of uncontrolled type 2 diabetes despite prior nutrition therapy; and stable dosing with a sulfonylurea for ≥ 8 weeks</p>	<p>N=105 24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, PPG, and post-prandial serum insulin; safety</p>	<p>Primary: Mean change in HbA_{1c} with miglitol was $-0.85 \pm 0.12\%$ compared to $-0.19 \pm 0.11\%$ with placebo ($P < 0.001$).</p> <p>Secondary: No significant differences in the changes in FPG and post-prandial serum insulin were observed ($P = 0.052$ and $P = 0.364$).</p> <p>There was a significant difference in the change in PPG between the two treatments ($P < 0.001$).</p> <p>Among the population, 49 (94.2%) patients receiving miglitol and 42 (79.3%) patients receiving placebo experienced at least one adverse event during the trial. A total of 59 and 39 adverse events occurred with miglitol and placebo, respectively. The most frequently reported adverse events were abdominal discomfort, diarrhea, hypoglycemia, and other; and there were no differences in the incidences of these events between the two treatments.</p>
<p>Standl et al.⁴⁹ (2001)</p> <p>Miglitol 25 mg to</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 30 to 70</p>	<p>N=154 24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p>	<p>Primary: Miglitol produced a significant reduction in HbA_{1c} (-0.55%; $P = 0.04$) and PPG (-2.6 mmol/L; $P = 0.0009$) compared to placebo.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>100 mg TID, glibenclamide* 3.5 to 5 mg BID to QID, and metformin 500 to 850 mg daily</p> <p>vs</p> <p>glibenclamide* 3.5 to 5 mg BID to QID, metformin 500 to 850 mg daily, and placebo</p>	<p>years of age with type 2 diabetes for ≥ 3 years; HbA_{1c} ≥ 7.5 to $\leq 10.5\%$; BMI ≤ 35 kg/m²; stable body weight over the previous 3 months; and inadequately controlled on combination therapy of diet, glibenclamide* and metformin</p>		<p>Secondary: FPG, PPG, fasting and postprandial serum insulin, TG, urinary glucose</p>	<p>Secondary: FPG decreased with miglitol and was almost unchanged with placebo; the difference was not significant (P=0.10).</p> <p>Fasting insulin levels were unchanged with both treatments throughout the trial, with no significant difference between them (P=0.79).</p> <p>Postprandial insulin decreased from baseline to trial end, but the difference between the groups was not significant (P=0.26).</p> <p>Postprandial TG decreased slightly with miglitol and remained unchanged with placebo, and the difference was not significant (P=0.47).</p>
<p>Van Gaal et al.⁵⁰ (2001)</p> <p>Miglitol 25 to 100 mg TID and metformin 500 mg TID or 850 mg BID or TID</p> <p>vs</p> <p>metformin 500 mg TID or 850 mg BID or TID and placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 30 to 75 years of age with type 2 diabetes for ≥ 1 year, HbA_{1c} ≥ 7.5 to $\leq 10.5\%$, BMI 23 to 40 kg/m², stable body weight over the previous 3 months, and whose diabetes was inadequately controlled by diet and metformin</p>	<p>N=152</p> <p>32 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in FPG, PPG, serum insulin, fasting and one-hour postprandial TG levels</p>	<p>Primary: There was a significant decrease in HbA_{1c} with miglitol compared to placebo (-0.21 vs 0.22%; P=0.011).</p> <p>Secondary: PPG decreased with both treatments, but the reduction was more significant with miglitol (from 16.5\pm3.8 mmol/L at baseline to 13.8\pm5.0 mmol/L at trial end) compared to placebo (from 16.3\pm3.4 mmol/L at baseline to 15.7\pm3.8 mmol/L at trial end). The baseline adjusted means were 13.8 mmol/L with miglitol vs 15.8 mmol/L with placebo (P=0.0007).</p> <p>Fasting insulin levels decreased more with miglitol compared to placebo, the difference was not significant (P value not reported).</p> <p>FPG, fasting and postprandial TG levels showed a descriptive advantage for miglitol, but did not reach a statistical difference. Mean FPG levels fell more with miglitol (baseline, 11.5\pm2.7 mmol/L; end of treatment, 10.8\pm3.6 mmol/L) compared to placebo (baseline, 11.6\pm3.1 mmol/L; end of treatment, 11.5\pm3.4 mmol/L; difference of adjusted means; P=0.15). Fasting TG levels fell with miglitol (treatment effect, -16.3 mg/dL) compared to placebo (treatment effect, 3.77 mg/dL; P=0.26). Similar results were seen for postprandial TG.</p>
<p>Chiasson et al.⁵¹</p>	<p>DB, MC, PC, RCT</p>	<p>N=324</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2001)</p> <p>Miglitol 100 mg TID</p> <p>vs</p> <p>metformin 500 mg TID</p> <p>vs</p> <p>miglitol 100 mg TID plus metformin 500 mg TID</p> <p>vs</p> <p>placebo</p>	<p>Patients >40 years of age with type 2 diabetes inadequately controlled by diet alone, HbA_{1c} 7.2 to 9.5%</p>	<p>36 weeks</p>	<p>Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and PPG, insulin levels, and TG</p>	<p>Mean change in HbA_{1c} from baseline was 0.38±0.12% with placebo, 0.02±0.10% with miglitol, -0.85±0.12% with metformin, and -1.39±0.11% with combination therapy. A reduction in mean placebo-subtracted HbA_{1c} of -1.78% was seen with combination therapy, and this was significantly different from metformin (-1.25%; P=0.002).</p> <p>Mean reductions in HbA_{1c} compared to placebo were -0.37% with miglitol, -1.25% with metformin, and -1.78% with combination therapy. The end of treatment mean HbA_{1c} was 8.5% with placebo, 8.2% with miglitol, 7.3% with metformin, and 6.9% with combination therapy. Significantly more patients (P=0.0014) receiving combination therapy (70.6%) were classified as responders (i.e., showed ≥15% reduction from baseline in HbA_{1c} or achieved an HbA_{1c} <7.0%) compared to metformin (45.5%).</p> <p>Secondary: Combination therapy resulted in better metabolic control compared to metformin for FPG (P=0.0025) and two-hour PPG AUC (P=0.0001).</p> <p>Changes in TG levels from baseline to trial end did not differ significantly between combination therapy compared to metformin, and showed no consistent trend (P value not reported).</p>
<p>Kheirbek et al.⁵² (2013)</p> <p>Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide,</p>	<p>OS, RETRO</p> <p>Veterans with diabetes cared for at a Veterans Administration Capital area medical center</p>	<p>N=17,773</p> <p>Variable duration</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Not reported</p>	<p>Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use				Secondary: Not reported
Mearns et al. ⁵³ (2015) Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)	Network MA (62 RCTs) Patients with inadequately controlled type 2 diabetes on metformin alone	N=32,185 3 to 12 months	Primary: Changes in HbA _{1c} , body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	Primary: All agents significantly reduced HbA _{1c} vs placebo; although, not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported

*Synonym for glyburide.

†Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times a day, TID=three times daily, XL=extended-release

Study abbreviations: AC=active comparator, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group,

PRO=prospective, RCT=randomized controlled trial, SA=single arm, SR=systematic review, XO=crossover

Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, DBP=diastolic blood pressure, DPP-4=dipeptidyl peptidase-4; FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, HbA_{1c}=glycosylated hemoglobin, HOMA-B=homeostasis model assessment-beta cell function, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HDL-C=high density lipoprotein cholesterol, HR=hazard ratio, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, M value=insulin sensitivity, NPH=neutral protamine Hagedorn, PPG=postprandial plasma glucose, RR=risk ratio, SBP=systolic blood pressure, SGLT2= Sodium-glucose co-transporter 2, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione, V_{02MAX}=regional fat distribution, WHO=World Health Organization

Additional Evidence

Dose Simplification

One small study by Aoki et al. concluded that the effects of alpha-glucosidase inhibitors on glycosylated hemoglobin (HbA_{1c}) were similar to those who took it prior to meals (as recommended) and those who took it after meals. Thirty-one type 2 diabetic patients who had never been treated with insulin injections or alpha-glucosidase inhibitors were randomized into two groups. One group took miglitol prior to meals, and the other group took miglitol after meals. After three months, the reduction in HbA_{1c} between the two groups was similar. The authors concluded that for those patients who could not remember to take their alpha-glucosidase inhibitor prior to meals could do so after their meal without a noticeable difference in HbA_{1c}.⁵⁴

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 9. Relative Cost of the Alpha-Glucosidase Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Acarbose	tablet	Precose®*	\$\$	\$\$
Miglitol	tablet	Glyset®*	\$\$\$\$\$	\$\$\$\$

*Generic is available in at least one dosage form or strength.

N/A=Not available

X. Conclusions

The alpha-glucosidase inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹⁻² **Acarbose and miglitol are available in a generic formulation.**

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin (HbA_{1c}) will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore,

advantages and disadvantages of specific antidiabetic agents for each patient should be considered. In general, the α -glucosidase inhibitors are not recommended for use in the management of patients with a high HbA_{1c} (7.6 to 9.0%), mainly due to the limited HbA_{1c} lowering potential associated with the medication class compared to other available antidiabetic medications. The α -glucosidase inhibitors may be utilized as monotherapy in the management of patients with a low HbA_{1c} (6.5 to 7.5%); however, metformin remains the most appropriate initial choice for monotherapy in all patients. In addition, clinical guidelines recognize the potential use of α -glucosidase inhibitors when postprandial hyperglycemia is present. Among all current clinical guidelines, preference of one α -glucosidase inhibitor over another is not stated.³⁻¹²

A variety of clinical trials have been conducted with the alpha-glucosidase inhibitors. A clinical trial directly comparing acarbose and miglitol does not evaluate glycemic control among type 2 diabetics; rather the results demonstrate that there is no significant difference between the two agents with regards to glucose variability during pre- and post-prandial periods.³⁵ The majority of the clinical trials have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.^{22-25,33-34,42-43,45,47-51} When comparing similar monotherapy treatment regimens, sulfonylureas have been shown to be more effective than the alpha-glucosidase inhibitors.^{28,30}

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the alpha-glucosidase inhibitors or any other antidiabetic drug.^{1,2}

There is insufficient evidence to support that one brand alpha-glucosidase inhibitor is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand alpha-glucosidase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Precose® [package insert]. Wayne (NJ): Bayer HealthCare Pharmaceuticals Inc.; 2015 Mar.
2. Glyset® [package insert]. New York (NY): Pharmacia & Upjohn Co.; 2012 Aug.
3. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* 2016;39(Suppl. 1):S1–S112.
4. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012 Jun;35(6):1364-79.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2015 Mar;58(3):429-42.
6. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2012 Feb 7;156(3):218-31.
7. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract*. 2015 Apr;21 Suppl 1:1-87.
8. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. *Endocr Pract*. 2016;22(1):84-113.
9. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
10. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
11. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
12. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. *Pediatrics* 2013;131(2):364-382.
13. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.
14. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.
15. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. *Diabetes Care* 2014;37(7):2034-2054.
16. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Jan]. Available from: <http://www.thomsonhc.com/>.
17. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Jan 2017]. Available from: <http://online.factsandcomparisons.com>.
18. Chiasson J, Josse R, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. *JAMA*. 2003;290(4):486-94.
19. Chiasson J, Josse R, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. *Lancet*. 2002;359(9323):2072-7.
20. Van de Laar FA, Lucassen PLBJ, Akkermans RP, Van de Lisdonk EH, De Grauw WJC. Alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose (review). *Cochrane Database Syst Rev*. 2006 Oct 18;(4):CD005061.
21. Buse J, Hart K, Minasi L. The PROTECT study: final results of a large multicenter postmarketing study in patients with type 2 diabetes. *Clin Ther*. 1998 Mar-Apr;20(2):257-69.

22. Hwu C, Ho L, Fuh M, et al. Acarbose improves glycemic control in insulin-treated Asian type 2 diabetic patients: results from a multinational, placebo-controlled study. *Diabetes Res Clin Pr.* 2003;60(2):111-8.
23. Josse RG, Chiasson JL, Ryan EA, et al. Acarbose in the treatment of elderly patients with type 2 diabetes. *Diabetes Res Clin Pr.* 2003;59(1):37-42.
24. Lam KS, Tiu SC, Tsang MW, et al. Acarbose in NIDDM patients with poor control on conventional oral agents. *Diabetes Care.* 1998;21(7):1154-8.
25. Lin BJ, Wu HP, Huang HS, et al. Efficacy and tolerability of acarbose in Asian patients with type 2 diabetes inadequately controlled with diet and sulfonylureas. *J Diabetes Complications.* 2003;17(4):179-85.
26. Mori Y, Shiozaki M, Matsuura K, Tanaka T, Yokoyama J, Utsunomiya K. Evaluation of efficacy of acarbose on glucose fluctuation and postprandial glucose using continuous glucose monitoring in type 2 diabetes mellitus. *Diabetes Technol Ther.* 2011;13(4):467-70.
27. Jian-bin SU, Xue-qin W, Jin-feng C, Gang WU, Yan J. Glycemic variability in insulin treated type 2 diabetics with well-controlled hemoglobin A1c and its response to further treatment with acarbose. *Chin Med J.* 2011;124(1):144-7.
28. Feinbock C, Luger A, Klingler A, et al. Prospective multicenter trial comparing the efficacy of, and compliance with, glimepiride or acarbose treatment in patients with type 2 diabetes not controlled with diet alone. *Diabetes Nutr Metab.* 2003;16(4):214-21.
29. Zhou J, Li H, Zhang X, Peng Y, et al. Nateglinide and acarbose are comparably effective reducers of postprandial glycemic excursions in Chinese antihyperglycemic agent-naïve subjects with type 2 diabetes. *Diabetes Technology & Therapeutics* 2013;15(6):481-488.
30. van de Laar FA, Lucassen PL, Kemp J, van de Lisdonk EH, van Weel C, Rutten GE. Is acarbose equivalent to tolbutamide as first treatment for newly diagnosed type 2 diabetes in general practice? A randomized controlled trial. *Diabetes Res Clin Pr.* 2004 Jan;63(1):57-65.
31. Wagner H, Degerblad M, Thorell A, Nygren J, Ståhle A, Kuhl J, et al. Combined treatment with exercise training and acarbose improves metabolic control and cardiovascular risk factor profile in subjects with mild type 2 diabetes. *Diabetes Care.* 2006 July;29(7):1471-7.
32. de Luis Roman DA, del Pozo GE, Aller R, Romero BE, Conde VR. Usefulness of miglitol in patients with diabetes mellitus type 2 and insufficient control of blood glucose [abstract, in Spanish]. *Rev Clin Esp.* 2004;204(1):32-4.
33. Aoki K, Nakamura A, Ito S, Nezu U, Iwasaki T, Takahashi M, et al. Administration of miglitol until 30 min after the start of a meal is effective in type 2 diabetic patients. *Diabetes Res Clin Prac.* 2007;78:30-3.
34. Johnston PS, Lebovitz HE, Coniff RF, et al. Advantages of α -glucosidase inhibition as monotherapy in elderly type 2 diabetic patients. *J Clin Endocrinol Metab.* 1998;83(5):1515-22.
35. Tsujino D, Nishimura R, Taki K, Morimoto A, Tajima N, Utsunomiya K. Comparing the efficacy of α -glucosidase inhibitors in suppressing postprandial hyperglycemia using continuous glucose monitoring: a pilot study-the MAJOR study. *Diabetes Technol Ther.* 2011;13(3):303-8.
36. van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005 Apr 18;(2):CD003639.
37. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med.* 2007 Sep 18;147(6):386-9.
38. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005 Jul 20;(3):CD002966.
39. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2006 Oct 18;(4):CD006060.
40. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract.* 2008 Feb;79(2):196-203.
41. Zhang W, Kim D, Philip E, et al; GlucoVIP investigators. A multinational, observational study to investigate the efficacy, safety and tolerability of acarbose as add-on or monotherapy in a range of patients: the GlucoVIP study. *Clin Drug Investig* (2013) 33:263-274.
42. Halimi S, Le Berre MA, Grange V. Efficacy and safety of acarbose add-on therapy in the treatment of overweight patients with type 2 diabetes inadequately controlled with metformin: a double-blind, placebo-controlled study. *Diabetes Res Clin Pr.* 2000;50(1):49-56.
43. Phillips P, Karrasch J, Scott R, et al. Acarbose improves glycemic control in overweight type 2 diabetic patients insufficiently treated with metformin. *Diabetes Care.* 2003;26(2):269-73.
44. Bayraktar M, Van Thiel D, Adalar N. A comparison of acarbose versus metformin as an adjuvant therapy in sulfonylurea-treated NIDDM patients. *Diabetes Care.* 1996;19(3):252-4.

45. Bao YQ, Zhou J, Zhou M, Cheng UJ, Lu W, Pan XP, et al. Glipizide controlled-release tablets, with or without acarbose, improve glycemic variability in newly diagnosed type 2 diabetes. *Clinical and Experimental Pharmacology and Physiology*. 2010;37:564-8.
46. Lopez-Alvarenga JC, Aguilar-Salinas CA, Velasco-Perez ML, et al. Acarbose vs bedtime NPH insulin in the treatment of secondary failures to sulphonylurea-metformin therapy in type 2 diabetes mellitus. *Diabetes Obes Metab*. 1999;1(1):29-35.
47. Nemoto M, Tajima N, Kawamori R. Efficacy of combined use of miglitol in type 2 diabetes patients receiving insulin therapy-placebo-controlled double-blind comparative study. *Acta Diabetol*. 2011;48:15-20.
48. Hsieh SH, Shih KC, Chou CW, Chu CH. Evaluation of the efficacy and tolerability of miglitol in Chinese patients with type 2 diabetes mellitus inadequately controlled by diet and sulfonylureas. *Acta Diabetol*. 2011;48:71-7.
49. Standl E, Schernthaner G, Rybka J, et al. Improved glycemic control with miglitol in inadequately-controlled type 2 diabetics. *Diabetes Res Clin Pr*. 2001;51(3):205-13.
50. Van Gaal L, Maislos M, Schernthaner G, et al. Miglitol combined with metformin improves glycemic control in type 2 diabetes. *Diabetes Obes Metab*. 2001;3(5):326-31.
51. Chiasson J, Naditch L. The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. *Diabetes Care*. 2001;24(6):989-94.
52. Kheirbek RE, Alemi F, Zargoush M. Comparative effectiveness of hypoglycemic medications among veterans. *J Manag Care Pharm*. 2013;19(9):740-44.
53. Mearns ES, Sobieraj DM, White CM, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One*. 2015 Apr 28;10(4):e0125879.
54. Aoki K, Nakajima S, Nezu U, et al. Comparison of pre- vs postmeal administration of miglitol for 3 months in type 2 diabetic patients. *Diabetes Obes Metab* 2008 Sep;10(10): 970-2.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Amylinomimetics
AHFS Class 682003
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Pramlintide is the only amylinomimetic agent that is currently available. It is approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes mellitus who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.¹⁻³ Amylin is co-secreted with insulin by pancreatic beta cells in response to food intake. It affects postprandial glucose levels by slowing gastric emptying, suppressing glucagon secretion, and regulating food intake via modulation of appetite.¹ Patients with type 1 and type 2 diabetes have dysfunctional beta cells, which leads to a reduced secretion of insulin and amylin in response to food.¹ Pramlintide is a synthetic analog of human amylin, which has been shown to modulate gastric emptying, decrease postprandial glucagon concentrations in patients using insulin, and reduce caloric intake.¹⁻³

The amylinomimetics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available. This class was last reviewed in February 2015.

Table 1. Amylinomimetics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Pramlintide	injection	SymlinPen [®]	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Amylinomimetics

Clinical Guideline	Recommendation(s)
American Diabetes Association: Standards of Medical Care in Diabetes (2016) ⁴	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) \geq6.5%, or a fasting plasma glucose (FPG) \geq126 mg/dL, or a two-hour plasma glucose \geq200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose \geq200 mg/dL). <p>Prevention or delay of type 2 diabetes</p> <ul style="list-style-type: none"> An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to \geq150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. Metformin therapy for prevention of type 2 diabetes should be considered in

Clinical Guideline	Recommendation(s)
	<p>those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus.</p> <ul style="list-style-type: none"> • Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p><u>Glycemic goals in adults</u></p> <ul style="list-style-type: none"> • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p><u>Pharmacologic therapy for type 1 diabetes</u></p> <ul style="list-style-type: none"> • Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. • Most patients should use of insulin analogs to reduce hypoglycemia risk. • Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. <p><u>Pharmacologic therapy for type 2 diabetes</u></p> <ul style="list-style-type: none"> • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If the A_{1c} target is not achieved after approximately three months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • Pregestational Diabetes <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1c} <6.5%, to reduce

Clinical Guideline	Recommendation(s)
	<p>the risk of congenital anomalies.</p> <ul style="list-style-type: none"> ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. ● Gestational Diabetes Mellitus <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. ● General Principles for Management of Diabetes in Pregnancy <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. ● Due to increased red blood cell turnover, A_{1c} is lower in normal pregnancy than in normal nonpregnant women. The A_{1c} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012 and 2015 Update)⁵</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> ● Glycemic targets and glucose-lowering therapies must be individualized. ● Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. ● Unless there are prevalent contraindications, metformin is the optimal first line drug. ● After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. ● Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. ● All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. ● Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> ● It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. ● Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. ● Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.

Clinical Guideline	Recommendation(s)														
	<ul style="list-style-type: none"> • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> • Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. • Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. • In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. • Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. <p>Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations</p> <table border="1" data-bbox="505 1717 1409 1902"> <tbody> <tr> <td data-bbox="505 1717 691 1745">Initial Drug</td> <td data-bbox="691 1717 1409 1745">Metformin</td> </tr> <tr> <td data-bbox="505 1745 691 1772">Monotherapy</td> <td data-bbox="691 1745 1409 1772"></td> </tr> <tr> <td data-bbox="505 1772 691 1799">Efficacy (↓HbA_{1c})</td> <td data-bbox="691 1772 1409 1799">High</td> </tr> <tr> <td data-bbox="505 1799 691 1827">Hypoglycemia</td> <td data-bbox="691 1799 1409 1827">Low risk</td> </tr> <tr> <td data-bbox="505 1827 691 1854">Weight</td> <td data-bbox="691 1827 1409 1854">Neutral/loss</td> </tr> <tr> <td data-bbox="505 1854 691 1881">Side Effects</td> <td data-bbox="691 1854 1409 1881">Gastrointestinal/lactic acidosis</td> </tr> <tr> <td colspan="2" data-bbox="505 1881 1409 1902">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug</td> </tr> </tbody> </table>	Initial Drug	Metformin	Monotherapy		Efficacy (↓HbA _{1c})	High	Hypoglycemia	Low risk	Weight	Neutral/loss	Side Effects	Gastrointestinal/lactic acidosis	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug	
Initial Drug	Metformin														
Monotherapy															
Efficacy (↓HbA _{1c})	High														
Hypoglycemia	Low risk														
Weight	Neutral/loss														
Side Effects	Gastrointestinal/lactic acidosis														
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug															

Clinical Guideline	Recommendation(s)						
	combination therapy (order not meant to denote any specific preference)						
	Two Drug Combinations	Metformin + sulfonamide	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)
	Efficacy (HbA _{1c})	High	High	Intermediate	Intermediate	High	Highest
	Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk
	Weight	Gain	Gain	Neutral	Loss	Loss	Gain
	Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia
	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)						
	Three Drug Combinations	Metformin + sulfonamide +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + SGLT2 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +
		TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonamide, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonamide, TZD, SGLT2 inhibitor, or insulin	Sulfonamide, TZD, DPP-4 inhibitor, or insulin	Sulfonamide, TZD, or insulin	TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist
	If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents						
More Complex Insulin Strategies	Combination injectable therapy						
American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012) ⁶	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. 						
American Association of Clinical Endocrinologists/ American College Of Endocrinology: Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015) ⁷	<p>Antihyperglycemic pharmacotherapy for type 2 diabetes</p> <ul style="list-style-type: none"> The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement. Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. 						

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. • The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. • When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists: Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm 2016 (2016)⁸</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} \leq6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • The therapeutic regimen should be as simple as possible to optimize adherence. <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of

Clinical Guideline	Recommendation(s)
	<p>patients.</p> <ul style="list-style-type: none"> • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ Sodium glucose cotransporter 2 (SGLT-2) inhibitors. ○ DPP-4 inhibitors. ○ . ○ TZDs (use with caution). ○ Alpha-glucosidase inhibitors. • sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ DPP-4 inhibitors. ○ TZD. ○ Basal insulin. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Three-drug combination therapy</u></p> <ul style="list-style-type: none"> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfoarea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p>Insulin therapy algorithm</p> <ul style="list-style-type: none"> ● Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. ● Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. ● Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. ● Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <p>Basal insulin</p> <ul style="list-style-type: none"> ● Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. ● Titrate insulin dose every two to three days to reach glycemic goals. ● Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. ● Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p>Basal-bolus insulin regimens</p> <ul style="list-style-type: none"> ● Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. ● A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. ● Doses of insulin may be titrated every two to three days to reach glycemic goals. <p>Basal insulin and incretin therapy regimens</p> <ul style="list-style-type: none"> ● Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. ● The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last updated July 2016)⁹</p>	<p>Individualized care</p> <ul style="list-style-type: none"> ● Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop

Clinical Guideline	Recommendation(s)
10	<p>any medicines that are not effective.</p> <ul style="list-style-type: none"> • Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p><u>HbA_{1c} targets</u></p> <ul style="list-style-type: none"> • Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. • For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. • In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> ○ reinforce advice about diet, lifestyle and adherence to drug treatment and ○ support the person to aim for an HbA_{1c} level of 7.0% and ○ intensify drug treatment. • Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> ○ who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy ○ for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job ○ for whom intensive management would not be appropriate, for example, people with significant comorbidities. • If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p><u>Drug treatment</u></p> <ul style="list-style-type: none"> • For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost • If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. • Initial drug treatment <ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below

Clinical Guideline	Recommendation(s)
	<p>45 ml/minute/1.73m²;</p> <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². <ul style="list-style-type: none"> ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p>First intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. • Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes. <p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment. • If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. • Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in 6 months). • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated,

Clinical Guideline	Recommendation(s)
	<p>and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment.</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p><u>Insulin-based treatments</u></p> <ul style="list-style-type: none"> • When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional. • When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. • Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation. ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: <ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals. ○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes: <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. • Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). • Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)¹¹</p>	<ul style="list-style-type: none"> • Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. • Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes (2012)¹²</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> • Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. • Match the timing of medication (including insulin) and meals. • Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. • Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals. • Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. • Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity.

Clinical Guideline	Recommendation(s)
	<p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> • Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. • A lower HbA_{1c} target may be considered if it is easily and safely achieved. • A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> • Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. • Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. • First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. • Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. • Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering medications (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin

Clinical Guideline	Recommendation(s)
	<p>(biphasic insulin).</p> <ul style="list-style-type: none"> • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)¹³</p>	<ul style="list-style-type: none"> • Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations ≥ 250 mg/dL. ○ Whose HbA_{1c} is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
<p>National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November 2016)¹⁴</p>	<p>Education and information for children and young people with type 1 diabetes</p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. • Tailor the education programme to each child or young person with type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. • Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Encourage children and young people with type 1 diabetes to wear or carry something that identifies them as having type 1 diabetes (e.g., a bracelet). • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. • Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations. • Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p><u>Insulin therapy for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. • Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen. • Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. • Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. • Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin infusion users. • Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. • Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin (0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%. • Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. • Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. • Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with type 1 diabetes a review of injection sites at each clinic visit. • Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. • If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily injections, continuous subcutaneous insulin infusion [CSII or insulin pump] therapy or once-, twice- or three-times daily mixed insulin injections). <p><u>Oral medicines for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control.

Clinical Guideline	Recommendation(s)
	<p><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. • Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. • Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. • Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain. <p><u>Education and information for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ HbA_{1c} monitoring and targets ○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control ○ the aims of metformin therapy and possible adverse effects ○ the complications of type 2 diabetes and how to prevent them. • Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every 2 years. • Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. <p><u>Dietary management for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • At each contact with a child or young person with type 2 diabetes who is

Clinical Guideline	Recommendation(s)
	<p>overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this.</p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. • At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. • Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications. • Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. • Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. • At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI. • Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. • Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy. <p><u>Metformin</u></p> <ul style="list-style-type: none"> • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management (Published 2015; last updated July 2016)¹⁵</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> • Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. • Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target. • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles ○ total glycated hemoglobin estimation (if abnormal hemoglobins). • Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. • Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia. • Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p><u>Self-monitoring of blood glucose</u></p> <ul style="list-style-type: none"> • Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least four times a day, including before each

Clinical Guideline	Recommendation(s)
	<p>meal and before bed.</p> <ul style="list-style-type: none"> • Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). • Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia. • Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. • Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy) • Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking. <p><u>Continuous glucose monitoring</u></p> <ul style="list-style-type: none"> • Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. • Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause. ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level ≥9%) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in HbA_{1c} of 2.5% or more. • For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. <p><u>Insulin regimens</u></p> <ul style="list-style-type: none"> • Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. • Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only).

Clinical Guideline	Recommendation(s)
	<p><u>Long-acting insulin</u></p> <ul style="list-style-type: none"> • Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. • Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul style="list-style-type: none"> ○ an existing insulin regimen being used by the person that is achieving their agreed targets ○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. • Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p><u>Rapid-acting insulin</u></p> <ul style="list-style-type: none"> • Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. • Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. • If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. <p><u>Mixed insulin</u></p> <ul style="list-style-type: none"> • Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. • Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p><u>Optimizing insulin therapy</u></p> <ul style="list-style-type: none"> • For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously optimized insulin regimen, the following should be considered: <ul style="list-style-type: none"> ○ injection technique ○ injection sites ○ self-monitoring skills ○ knowledge and self-management skills ○ nature of lifestyle ○ psychological and psychosocial difficulties ○ possible organic causes such as gastroparesis. • Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. <p><u>Adjuncts</u></p> <ul style="list-style-type: none"> • Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> • Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using

Clinical Guideline	Recommendation(s)
	<p>one or more types of insulin injection pen.</p> <ul style="list-style-type: none"> • Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. • Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. • After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. • Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. • Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. • Check injection site condition at least annually and if new problems with blood glucose control occur.
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)¹⁶</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> • Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. • If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <p><u>Glycemic control goals</u></p> <ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%)

Clinical Guideline	Recommendation(s)
	<p>for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment.</p> <ul style="list-style-type: none"> • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p> <ul style="list-style-type: none"> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the amylinomimetics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Amylinomimetics¹

Indication	Pramlintide
Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy	✓
Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy	✓

IV. Pharmacokinetics

The pharmacokinetic parameters of the amylinomimetics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Amylinomimetics¹⁻³

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Half-Life (hours)
Pramlintide	30 to 40	Not extensively protein bound	Renal	0.50 to 0.83

V. Drug Interactions

There are no significant drug interactions reported with the amylinomimetics.¹⁻³ Due to its effects on gastric emptying, pramlintide should not be considered for patients taking drugs that alter gastrointestinal motility (e.g., anticholinergic agents) and agents that slow the intestinal absorption of nutrients (e.g., alpha-glucosidase inhibitors).¹ Pramlintide has the potential to delay the absorption of concomitantly administered oral medications. When the rapid onset of a concomitant administered oral agent is a critical determinant of effectiveness, the agent should be administered at least one hour prior to or two hours after pramlintide injection.¹

VI. Adverse Drug Events

The most common adverse drug events reported with the amylinomimetics are listed in Table 5. The boxed warning for pramlintide is listed in Table 6. When used alone, pramlintide does not cause hypoglycemia; however, when co-administered with insulin, there is an increased risk of insulin-induced severe hypoglycemia. Severe hypoglycemia occurs within the first three hours following administration of pramlintide.

Table 5. Adverse Drug Events (%) Reported with the Amylinomimetics¹⁻³

Adverse Event	Pramlintide*
Central Nervous System	
Dizziness	2 to 6
Fatigue	3 to 7
Headache	5 to 13
Gastrointestinal	
Abdominal pain	2 to 8
Anorexia	0 to 17
Nausea	28 to 48
Vomiting	7 to 11
Respiratory	
Coughing	2 to 6
Pharyngitis	3 to 5
Other	
Allergic reaction	<1 to 6
Arthralgia	2 to 7
Inflicted injury	8 to 14
Severe hypoglycemia (medically assisted)	0.4 to 7.3
Severe hypoglycemia (patient-ascertained)	0.6 to 16.8

*In combination with insulin therapy.

Table 6. Boxed Warning for the Amylinomimetics¹⁻³

WARNING
Pramlintide is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with pramlintide use occurs, it is seen within three hours following a pramlintide injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

VII. Dosing and Administration

The usual dosing regimens for the amylinomimetics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Amylinomimetics¹⁻³

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Pramlintide	<p><u>Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy:</u> Multi-dose pen: initial, 15 µg SC immediately prior to major meals; maintenance, 30 to 60 µg SC immediately prior to major meals</p> <p><u>Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy:</u> Multi-dose pen: initial, 60 µg SC immediately prior to major meals; maintenance, 60 to 120 µg SC immediately prior to major meals</p>	Safety and efficacy in children have not been established.	Pen injector: 2700 µg/ 2.7 mL 1500 µg/ 1.5 mL

SC=subcutaneous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the amylinomimetics are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Amylinomimetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 1 Diabetes				
Edelman et al. ¹⁷ (2006) Pramlintide 15 to 60 µg with meals and insulin (existing regimen) vs placebo and insulin (existing regimen)	DB, MC, PC, RCT Type 1 diabetic patients <18 years of age with an HbA _{1c} 7.5 to 9.0%, intensely or continuously treated with insulin for the past year, and with no severe hypoglycemic event over the preceding 6 months	N=296 29 weeks	Primary: Safety Secondary: Change from baseline in HbA _{1c} , PPG concentrations, insulin, and weight; tolerability	Primary: Both treatments resulted in a similar number of nonsevere hypoglycemic events. The event rate per patient years was 0.57 with pramlintide compared to 0.30 with placebo (P<0.05). Secondary: Baseline HbA _{1c} was 8.1% with both treatments and at week 29 had decreased comparably (-0.50; 95% CI, -0.61 to -0.33 vs -0.50%; 95% CI, -0.63 to -0.35; P value not reported). Among pramlintide-treated patients, a significantly greater number were able to achieve a PPG concentration of 9.9 mmol/L at breakfast (68 vs 51%), lunch (71 vs 61%), and dinner (70 vs 58%; P<0.0001 for each meal). At week 29 the total insulin dose with pramlintide decreased by -12% compared to an increase of 1% with placebo. Between weeks 0 through 29, the reduction in body weight was significant with pramlintide compared to placebo (-1.3 vs 1.2 kg; P<0.0001). Reduced appetite, vomiting, and sinusitis occurred at twice the level with pramlintide compared to placebo (P<0.01).
Whitehouse et al. ¹⁸ (2002) Pramlintide 30 to 60 µg QID and insulin (existing regimen)	DB, PC, RCT Type 1 diabetic patients	N=480 52 weeks	Primary: Change from baseline HbA _{1c} Secondary: Change from baseline HbA _{1c} and body weight at	Primary: Significantly greater reductions in HbA _{1c} were observed with pramlintide (-0.39%) compared to placebo (-0.12%; P=0.0071) at 52 weeks. Secondary: Significantly greater reductions in HbA _{1c} with pramlintide were achieved at weeks 13 (-0.67 vs -0.16%; P<0.0001), 26 (-0.58 vs -0.18%; P=0.0001), and 52 (-0.39 vs -0.12%; P=0.0071).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo and insulin (existing regimen)			weeks 13, 26, and 52	<p>Pramlintide-treated patients had sustained reductions in body weight that were significantly different compared to placebo-treated patients (P<0.001) from week 13 onward (data reported in graphical form only).</p> <p>The most commonly reported side effects with pramlintide were nausea (46.5 vs 21.9%; P values not reported) and anorexia (17.7 vs 2.1%; P values not reported). Withdrawal due to adverse event(s) occurred in 31 (12.8%) and 19 (8.0%) pramlintide- and placebo-treated patients.</p>
Ratner et al. ¹⁹ (2004) Pramlintide 60 µg TID, 60 µg QID, or 90 µg TID and insulin (existing regimen) vs placebo and insulin (existing regimen)	DB, PC, RCT Type 1 diabetics	N=651 52 weeks	Primary: Change from baseline HbA _{1c} at week 26 Secondary: Change from baseline HbA _{1c} at week 52, proportion of patients achieving HbA _{1c} <7.0%, safety	<p>Primary: Significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg TID compared to placebo (-0.41 vs -0.18%; P=0.012) after 26 weeks. In addition, significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg QID compared to placebo (-0.39 vs -0.18%; P=0.013).</p> <p>Secondary: Significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg TID compared to placebo (-0.29 vs -0.04%; P=0.011) after 52 weeks. In addition, significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg QID compared to placebo (-0.34 vs -0.04%; P=0.001).</p> <p>A threefold greater proportion of pramlintide-treated patients achieved HbA_{1c} <7.0% compared to placebo treated patients (P value not reported; data was reported in graphical form only). Pramlintide 90 µg was excluded from the analysis when results from a separate trial indicated the dose had an adverse tolerability profile. Patients originally randomized to this treatment continued to receive 90 µg to preserve the trial design.</p> <p>During the first four weeks of therapy, pramlintide-treated patients had a fourfold increase in severe hypoglycemic event rate compared to placebo-treated subjects (3.78 vs 0.87 events/year; no P value reported). The most commonly reported adverse event with pramlintide was nausea. Withdrawal due to adverse event(s) occurred in 38 (22.1%) patients receiving pramlintide 90 µg TID, 22 (13.7%) patients receiving pramlintide 60 µg QID, 32 (19.5%) patients receiving pramlintide 60 µg</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Marrero et al.²⁰ (2007)</p> <p>Pramlintide 15 to 60 µg with meals and insulin (existing regimen)</p> <p>vs</p> <p>placebo and insulin (existing regimen)</p>	<p>Post hoc analysis</p> <p>Type 1 diabetic patients who completed a 29 week DB, noninferiority, dose-finding pramlintide trial</p>	<p>N=266</p> <p>29 weeks</p>	<p>Primary: Patient response to satisfaction questionnaire</p> <p>Secondary: Not reported</p>	<p>T1D, and six (3.9%) patients receiving placebo.</p> <p>Primary: For the following topics the survey ratings favored pramlintide: Study medication (1) “made my blood glucose control more even or predictable,” (2) “provided me with more flexibility in what I can eat,” (3) “made it easier to control my weight,” and (4) “made it easier to control my appetite” (P<0.05 for all).</p> <p>There was no difference between treatments in the response to the following statements: Study medication (1) “made it easier to avoid low blood sugar reactions (hypoglycemia)” and (2) “I would like to continue taking the study medication” (P value not significant).</p> <p>Secondary: Not reported</p>
<p>Ratner et al.²¹ (2005)</p> <p>Pramlintide and insulin (existing regimen)</p> <p>vs</p> <p>placebo and insulin (existing regimen)</p>	<p>MA (3 trials)</p> <p>Type 1 diabetic patients with HbA_{1c} 7.0 to 8.5%</p>	<p>N=477</p> <p>26 weeks</p>	<p>Primary: Change from baseline in HbA_{1c} and body weight, adverse events (hypoglycemia)</p> <p>Secondary: Not reported</p>	<p>Primary: Significant baseline reductions in HbA_{1c} (-0.3%) and body weight (-1.8 kg) at endpoint were achieved with pramlintide (P<0.0009 for both).</p> <p>The risk of severe hypoglycemia was 1.40 with pramlintide compared to 1.86 with placebo.</p> <p>Secondary: Not reported</p>
<p>Heptulla et al.²² (2009)</p> <p>Pramlintide 3 to 5 µg /hour as a basal dose and insulin infusion (existing regimen was reduced by 30%)</p>	<p>RCT</p> <p>Adolescents with type 1 diabetes mellitus on insulin pump therapy</p>	<p>N=13</p> <p>24 hours</p>	<p>Primary: PPG, glucagon, and insulin concentrations</p> <p>Secondary: Not reported</p>	<p>Primary: Postprandial hyperglycemia was reduced by 26% with pramlintide compared to placebo (P<0.008).</p> <p>Postprandial glucagon concentrations were suppressed with pramlintide compared to placebo (P<0.003).</p> <p>The plasma insulin concentrations were unchanged.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin infusion (existing regimen)				Not reported
Type 2 Diabetes				
Singh-Franco et al. ²³ (2011) Pramlintide 120 to 150 µg SC BID or TID with meals	MA (8 trials) Type 2 diabetic patients (4 trials) and obese patients without diabetes (4 trials)	N=1,616 6 to 52 weeks	Primary: Change from baseline in HbA _{1c} Secondary: Likelihood of achieving HbA _{1c} ≤7.0%; change from baseline in FPG, PPG, and weight	Primary: Pooled analysis revealed that compared to placebo, pramlintide was associated with a baseline reduction in HbA _{1c} of -0.33% (P=0.0004). Secondary: After 52 weeks, pramlintide-treated patients were 1.52 times (95% CI, 0.83 to 2.78) more likely to achieve an HbA _{1c} ≤7.0% compared to placebo treated patients; however, this difference was not significant (P=0.18). Treatment with pramlintide was associated with a reduction from baseline in FPG of -6.34 mg/dL (95% CI, -24.96 to 12.28) over 24 weeks of treatment, but the difference was not significant (P=0.50). Treatment with pramlintide was associated with a reduction from baseline in PPG of -7.20 mg/dL (95% CI, -40.12 to 25.75) over 24 weeks of treatment, but the difference was not significant (P=0.67). Pramlintide was associated with a significant change in body weight in patients with type 2 diabetes compared to placebo (-2.21 kg; P<0.000001).
Karl et al. ²⁴ (2007) Pramlintide 120 µg before meals and insulin (existing regimen)	MC, OL Type 2 diabetics >18 years of age currently receiving insulin therapy with or without oral antidiabetics, and HbA _{1c} >7.0 to <11.0%	N=166 12 months (all results reported at 6 months)	Primary: Change from baseline in HbA _{1c} , FPG, PPG, body weight, and insulin; safety Secondary: Not reported	Primary: Pramlintide resulted in significant HbA _{1c} reductions at months three and six (-0.66 and -0.56%; P<0.05). At some point during the initial six months after initiating therapy, 28.1% of the patients who had a baseline HbA _{1c} >7.0% achieved an HbA _{1c} <7.0%. Compared to baseline, both fasting and PPG concentrations were significantly reduced (P<0.05). Significant baseline reductions in weight were noted at months three and six (-2.3 and -2.8 kg; P<0.05). At months three and six, mealtime and total insulin doses remained

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>significantly lower compared to baseline ($P<0.05$).</p> <p>Nausea (29.5%), vomiting (7.2%), and diarrhea (5.4%) were the most commonly reported adverse events. There was an overall incidence of 12% for hypoglycemia, with two patients experiencing severe hypoglycemia during the six month treatment period.</p> <p>Secondary: Not reported</p>
<p>Riddle et al.²⁵ (2007)</p> <p>Pramlintide 60 µg SC BID or TID with meals, titrated to 120 µg SC</p> <p>vs</p> <p>placebo</p> <p>All patients also received existing insulin regimens.</p>	<p>DB, MC, PC, RCT</p> <p>Type 2 diabetics 25 to 75 years of age not achieving adequate glycemic control with insulin glargine (no mealtime insulin), with or without oral antidiabetic therapy, and an $HbA_{1c} >7.0$ to 10.5% and BMI 25 to 45 kg/m²</p>	<p>N=212</p> <p>16 weeks</p>	<p>Primary: Change from baseline HbA_{1c} at week 16, proportion of patients meeting all of the following prespecified criteria at week 16: $HbA_{1c} \leq 7.0\%$ or an HbA_{1c} baseline reduction $\geq 0.5\%$, mean daily PPG increments ≤ 40 mg/dL, no weight gain, and no severe hypoglycemia</p> <p>Secondary: Individual components of the composite endpoint; proportion of patients achieving $HbA_{1c} \leq 7.0$ or</p>	<p>Primary: Pramlintide-treated patients experienced significantly greater baseline reductions in HbA_{1c} at week 16 compared to placebo-treated patients (-0.70 vs -0.36%; $P<0.05$).</p> <p>At week 16, significantly more pramlintide-treated patients achieved the composite endpoint compared to placebo-treated patients (25 vs 7%; $P<0.001$).</p> <p>Secondary: The proportion of patients who achieved an $HbA_{1c} \leq 7.0\%$ or who had a reduction in $HbA_{1c} \geq 0.5\%$ was not different between pramlintide and placebo (54 vs 45%; P value not reported).</p> <p>Significantly more pramlintide-treated patients achieved mean PPG increments ≤ 40 mg/dL ($P<0.0001$) and did not experience weight gain ($P<0.0001$) compared to placebo-treated patients.</p> <p>Compared to placebo-treated patients, more pramlintide-treated patients achieved both HbA_{1c} and PPG components ($P<0.005$), more patients reached the HbA_{1c} goal without weight gain ($P<0.0001$), and more patients had well controlled PPG without weight gain ($P<0.0001$).</p> <p>The proportion of patients achieving an $HbA_{1c} \leq 7.0$ or $\leq 6.5\%$ was 23 and 11% with pramlintide compared to 13 and 4% with placebo, respectively (P values not reported).</p> <p>The insulin glargine dosage increased steadily throughout the trial. The</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>≤6.5%; changes from baseline to each time point in HbA_{1c}, seven-point glucose profiles, PPG increments, FPG, weight, and insulin glargine dose</p>	<p>mean increase in insulin glargine dosage at week 16 was 11.7±1.9 and 13.1±1.6 units with pramlintide and placebo, respectively (P value not reported).</p> <p>The average change from baseline in FPG was -28.3 and -12.0 mg/dL at week 16 with pramlintide and placebo, respectively (P value not reported).</p> <p>At week 16, PPG was significantly decreased from baseline with pramlintide compared to placebo (-24.4 vs -0.4 mg/dL; P<0.0001).</p> <p>By week 16, pramlintide was associated with weight loss compared to weight gain with placebo (-1.6 vs 0.7 kg; P<0.0001) By the end of treatment, 68% of pramlintide-treated patients had lost weight compared to approximately 35% of placebo-treated patients (P<0.0001).</p>
<p>Hollander et al.²⁶ (2003)</p> <p>Pramlintide 60, 90, or 120 µg SC BID and insulin (existing regimen)</p> <p>vs</p> <p>placebo and insulin (existing regimen)</p> <p>Data for patients randomized to pramlintide 60 µg SC BID are not reported.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetics >18 years of age requiring insulin therapy for ≥ 6 months prior to trial initiation with an HbA_{1c} ≥8.0%, and without hypoglycemia in the 2 weeks preceding the trial</p>	<p>N=656</p> <p>12 months</p>	<p>Primary: Change from baseline in HbA_{1c} at week 26</p> <p>Secondary: Absolute change in HbA_{1c} at other time points, proportion of patients who achieved an HbA_{1c} <7.0 or <8.0%</p>	<p>Primary: After 26 weeks, pramlintide 120 µg was associated with a significant reduction in HbA_{1c} compared to placebo (-0.68; P<0.05), but no difference in the baseline reduction of HbA_{1c} was reported between the pramlintide 90 µg and placebo (-0.54%; P value not reported).</p> <p>Secondary: After 52 weeks, pramlintide 120 µg was associated with a significant baseline reduction in HbA_{1c} compared to placebo (-0.62; P<0.05), but no difference in the baseline reduction of HbA_{1c} was reported between pramlintide 90 µg and placebo (-0.35%; P value not reported).</p> <p>More patients receiving pramlintide (either dose) achieved an HbA_{1c} <7.0% compared to patients receiving placebo (9.4 and 12.2 vs 4.1%, respectively; P value not reported). Similarly, 42.4, 45.7, and 27.6% of patients receiving pramlintide 90 µg, pramlintide 120 µg, and placebo, respectively, achieved an HbA_{1c} <8.0% (P value not reported).</p>
<p>Ratner et al.²⁷ (2002)</p> <p>Pramlintide 30 to</p>	<p>DB, PC, RCT</p> <p>Type 2 diabetic patients</p>	<p>N=538</p> <p>52 weeks</p>	<p>Primary: Change in baseline HbA_{1c} and body weight at weeks</p>	<p>Primary: Significantly greater reductions in HbA_{1c} were achieved with pramlintide 75 µg compared to placebo (-0.9%; P=0.0004) after 13 weeks. In addition, HbA_{1c} was significantly lower for the majority of the study periods with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>150 µg TID and insulin (existing regimen)</p> <p>vs</p> <p>placebo and insulin (existing regimen)</p>			<p>13, 26, and 52</p> <p>Secondary: Proportion of patients achieving HbA_{1c} <7.0 or 8.0%, relative change of insulin use, safety</p>	<p>the exception of week 52 (P value not reported).</p> <p>Significantly greater reductions in HbA_{1c} were achieved with pramlintide 150 µg compared to placebo (-1.0%; P=0.0002). After 13 weeks, HbA_{1c} remained significantly lower for the rest of the trial (-0.6%; P=0.0068).</p> <p>Reductions in HbA_{1c} with pramlintide 30 µg were not different compared to placebo at any point during the trial.</p> <p>Significant baseline reductions (P<0.05) in body weight were achieved with all pramlintide doses throughout the trial when compared to placebo.</p> <p>Secondary: The proportions of patients achieving an HbA_{1c} <7.0% were 12.7, 13.4, and 19.2% in patients receiving pramlintide 30, 75, and 150 µg compared to 11.1% in patients receiving placebo (P values not reported).</p> <p>The proportions of patients achieving an HbA_{1c} <8.0% were 45.1, 46.4, and 54.0% in patients receiving pramlintide 30, 75, and 150 µg compared to 37.6% in patients receiving placebo (P values not reported).</p> <p>Insulin use increased with all treatments. With pramlintide, insulin use increased by 7.9 to 10.9%, while insulin use increased by 15.4% with placebo (P values not reported).</p> <p>The most commonly reported side effect with pramlintide was nausea.</p>
<p>Hollander et al.²⁸ (2003)</p> <p>Pramlintide 120 µg BID and insulin (existing regimen)</p> <p>vs</p> <p>placebo and insulin (existing regimen)</p>	<p>Post hoc analysis</p> <p>Type 2 diabetic patients who completed a 26 or 52 week, DB, PC, RCT</p>	<p>N=186</p> <p>26 and 52 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, body weight, insulin use, and the rate of severe hypoglycemia at week 26; safety</p> <p>Secondary: Not reported</p>	<p>Primary: At week 26, the difference in HbA_{1c} baseline reduction with pramlintide compared to placebo was -0.43% (P<0.0009). The proportion of patients who achieved an HbA_{1c} <7.0% at week 26 was 14% in the pramlintide group compared to 2% in the placebo group (P value was not reported).</p> <p>At week 26, the difference in weight baseline reduction with pramlintide compared to placebo was 2 kg (P<0.0003).</p> <p>No significant change in insulin dose or the number of insulin injections was noted between the treatments (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
regimen)				<p>At week 26, no significant difference was noted between the treatments in rates of severe hypoglycemia as reported in event rate per subject year (0.13 vs 0.19; P value not reported).</p> <p>No serious adverse events were reported with either treatment.</p> <p>Secondary: Not reported</p>
<p>Maggs et al.²⁹ (2003)</p> <p>Pramlintide 120 µg BID or pramlintide 150 µg TID and insulin (existing regimen)</p> <p>vs</p> <p>placebo and insulin (existing regimen)</p>	<p>Post hoc analysis</p> <p>Type 2 diabetic patients who completed a 52 week, DB, PC, RCT</p>	<p>N=410</p> <p>52 weeks</p>	<p>Primary: Change in baseline in HbA_{1c} and weight at week 52, safety</p> <p>Secondary: Not reported</p>	<p>Primary: A significantly greater baseline reduction in HbA_{1c} was achieved with pramlintide compared to placebo at week 52 (P<0.0001). This result was seen across the following ethnic groups: African Americans (-0.7%), Caucasians (-0.5%), and Hispanics (-0.3%).</p> <p>A significant baseline reduction in body weight was achieved with pramlintide compared to placebo at week 52 (-2.6 kg; P<0.0001).</p> <p>Nausea was more common with pramlintide, and hypoglycemia was reported to a similar extent with both treatments.</p> <p>Secondary: Not reported</p>
<p>Hollander et al.³⁰ (2004)</p> <p>Pramlintide 120 µg BID and insulin (existing regimen)</p> <p>vs</p> <p>placebo and insulin (existing regimen)</p>	<p>Post hoc analysis</p> <p>Type 2 diabetic patients who completed a 26 or 52 week, DB, PC, RCT</p>	<p>N=498</p> <p>26 and 52 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, insulin dose, and body weight</p> <p>Secondary: Not reported</p>	<p>Primary: At week 26, mean baseline reductions in HbA_{1c} with pramlintide compared to placebo (-0.59 vs -0.18%; P<0.0001).</p> <p>There was no difference in the change in total daily insulin requirements between the two treatments.</p> <p>At week 26, pramlintide-treated patients achieved a significant baseline reduction in weight compared to placebo (-1.5 vs 0.3 kg; P<0.0001).</p> <p>Secondary: Not reported</p>
<p>Riddle et al.³¹ (2009)</p>	<p>MC, OL</p>	<p>N=113</p>	<p>Primary: Proportion of</p>	<p>Primary: Thirty percent of pramlintide-treated patients achieved an HbA_{1c} ≤7%</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Pramlintide 120 µg prior to meals and basal insulin (QD to BID)</p> <p>vs</p> <p>rapid-acting insulin analogs 5 units before meals (titrated) and basal insulin (QD to BID)</p>	<p>Type 2 diabetic patients who were inadequately controlled using basal insulin and prior oral antihyperglycemic agents</p>	<p>24 weeks</p>	<p>patients achieving an HbA_{1c} ≤7.0%</p> <p>Secondary: Individual components of the composite end point, insulin dose, HbA_{1c}, change in HbA_{1c}, proportion of patients reaching HbA_{1c} ≤6.5%, FPG, PPG increments, changes in weight, changes in waist circumference, and adverse events including the incidence, severity, and time courses of hypoglycemia and nausea</p>	<p>compared to 11% of the patients receiving rapid-acting insulin analogs (P=0.018) with a similar dose of basal insulin.</p> <p>Secondary: Mean HbA_{1c} at 24 weeks was 7.2% with addition of pramlintide and 7.0% with addition of a rapid acting insulin analog. The least squares mean reduction of HbA_{1c} from baseline was -1.1% for pramlintide and -1.3% for rapid acting insulin analogs (P=0.46 between groups).</p> <p>HbA_{1c} ≤6.5% at 24 weeks was achieved by 29% of patients treated with pramlintide and by 34% of patients treated with a rapid-acting insulin analog (P=0.68 between groups).</p> <p>At week 24, mean weights were 106 kg (pramlintide) versus 109 kg (rapid-acting insulin analog). Least squares mean changes in weight from baseline were 0.0kg (pramlintide) versus 4.7 kg (rapid-acting insulin analog; P<0.0001).</p> <p>Differences in waist measurements were consistent with weight differences. Waist circumferences at week 24 were 115 cm and 120 cm for the pramlintide and rapid-acting insulin analog groups, respectively. Least squares mean changes in waist circumference from baseline were -0.6 cm and 2.2 cm, respectively (P=0.016)</p> <p>Similar basal insulin titration in both treatment arms resulted in similar mean FPG concentrations at week 24: 122 mg/dl (pramlintide) and 123 mg/dl (rapid-acting insulin analog) The least squares mean change of FPG from baseline was -31 mg/dl (pramlintide) and -34 mg/dl (rapid-acting insulin analog; P=0.65).</p> <p>An FPG concentration <100 mg/dl was achieved at week 24 by 30% of pramlintide-treated and 27% of rapid-acting insulin analog-treated patients (P=0.83).</p> <p>PPG increments were similar between study groups at week 24. No significant difference in the least squares mean change in postprandial increment from baseline to week 24 was found between treatment groups</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>(-17 mg/dl [pramlintide] vs -27 mg/dl [rapid-acting insulin analog]; P=0.17).</p> <p>The most common adverse events were hypoglycemia and nausea. Mild or moderate hypoglycemia occurred more frequently than nausea in both study groups and was observed in more patients treated with rapid acting insulin analog (82%) than with pramlintide (55%). Hypoglycemic events occurred more frequently in the pramlintide treatment group in the first 4 weeks but were more common in the rapid acting insulin analog treatment group from 18 to 24 weeks. Nausea was reported only in the pramlintide group (21%), most often early in treatment and declined over time.</p>

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, SC=subcutaneous, TID=three times daily

Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial

Miscellaneous abbreviation: BMI=body mass index, CI=confidence interval, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, PPG=post-prandial glucose

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 9. Relative Cost of the Amylinomimetics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Pramlintide	injection	SymlinPen®	\$\$\$\$\$	N/A

N/A=Not available

X. Conclusions

Pramlintide is the only amylinomimetic agent that is currently available. It is approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes mellitus who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.¹⁻³ It is not available in a generic formulation.

Several guidelines provide recommendations on the treatment of type 2 diabetes. According to the American Diabetes Association/ European Association for the Study of Diabetes treatment algorithm, metformin is recommended as first-line therapy, followed by a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin. Notably the higher the glycosylated hemoglobin (HbA_{1c}), the more likely insulin will be required.⁸ Pramlintide may be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight.⁷⁻⁸ In general, current clinical guidelines do not support the use of amylin analogs in the management of type 2 diabetes.

For the treatment of type 1 diabetes, the American Diabetes Association recommends the use of multiple dose insulin injections or continuous subcutaneous insulin infusion therapy.⁴ The addition of pramlintide to intensive insulin therapy should be considered to enhance glycemic control and to assist with weight management.^{9,16}

Several clinical trials have been conducted with pramlintide in patients with type 1 and type 2 diabetes mellitus.^{17-19,22,25-27} Data from clinical trials demonstrate that treatment with pramlintide is associated with significant baseline reductions in HbA_{1c} compared to treatment with placebo in type 1 and 2 diabetics already receiving insulin.¹⁷⁻³¹ Furthermore, treatment with pramlintide is associated with significant baseline reductions in fasting plasma glucose levels, post-prandial glucose levels, insulin use, and body weight.¹⁷⁻³¹ However, compared to other available antidiabetic agents, pramlintide is associated with modest HbA_{1c} lowering ability, and its use is often limited by adverse events.⁵

Pramlintide does not cause hypoglycemia when used alone; however, it is intended to be coadministered with insulin therapy. In this setting, pramlintide increases the risk of insulin-induced severe hypoglycemia, especially in patients with type 1 diabetes mellitus.¹ To minimize this risk, patients must be carefully selected, proper education must be provided, and glucose levels must be carefully monitored.¹ Therapy should only be considered in patients with insulin-using type 1 or type 2 diabetes who fulfill the following criteria: 1) have failed to achieve adequate glycemic control despite individualized insulin management; and 2) are receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes educator(s).¹

There is insufficient evidence to support that one brand amylinomimetic is safer or more efficacious than another within its given indication. Since pramlintide is only approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes mellitus, it should be managed through the existing medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand amylinomimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Symlin® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals, Inc.; February 2015.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Jan]. Available from: <http://www.thomsonhc.com/>.
3. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Jan 2017]. Available from: <http://online.factsandcomparisons.com>.
4. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2016;39(Suppl. 1):S1–S112.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015 Mar;58(3):429-42.
6. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.
7. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1:1-87..
8. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. Endocr Pract. 2016;22(1):84-113..
9. National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes. [guideline on the Internet]. London: NICE; 2009 May [cited 2014 Oct]. Available from: <http://www.nice.org.uk/guidance/cg87>.
10. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
11. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
12. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
13. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131(2):364-382.
14. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.
15. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.
16. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care 2014;37(7):2034-2054.
17. Edelman S, Garg S, Frias J, Maggs D, Wang Y, Strobel S, et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in Type 1 diabetes. Diabetes Care. 2006;29:2189-98.
18. Whitehouse F, Kruger DF, Fineman M, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. Diabetes Care. 2002;25(4):724-30.
19. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabet Med. 2004; 21(11):1204-12.
20. Marrero D, Crean J, Zhang B, Kellmeyer T, Gloster M, Herrmann K, et al. Effect of adjunctive pramlintide treatment on treatment satisfaction in patients with Type 1 diabetes. Diabetes Care. 2007;30:210-6.

21. Ratner R, Whitehouse F, Fineman S, Strobel S, Shen L, Maggs DG, et al. Adjunctive therapy with pramlintide lowers A1C without concomitant weight gain and increased risk of severe hypoglycemia in patients with Type 1 diabetes approaching glycemetic targets. *Exp Clin Endocrinol Diabetes*. 2005;113:199-204.
22. Heptulla RA, Rodriquez LM, Mason KJ, Haymond MW. Twenty-four-hour simultaneous basal-bolus administration of insulin and amylin in adolescents with type 1 diabetes decreased postprandial hyperglycemia. *J Clin Endocrinol Metab*. 2009;94:1608-11.
23. Singh-Franco D, Perez A, Harrington C. The effect of pramlintide acetate on glycemetic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2011 Feb;13(2):169-80.
24. Karl D, Philis-Tsimikas A, Darsow T, Lorenzi G, Kellmeyer T, Lutz K, et al. Pramlintide as an adjunct to insulin in patients with Type 2 Diabetes in a clinical practice setting reduced A1C, postprandial glucose excursions, and weight. *Diabetes Technol Ther*. 2007; 9(2):191-9.
25. Riddle M, Frias J, Zhang B, Maier H, Brown C, Lutz K, Kolterman O. Pramlintide improved glycemetic control and reduced weight in patients with type 2 diabetes using basal insulin. *Diabetes Care*. 2007 Nov;30(11):2794-9.
26. Hollander PA, Levy P, Fineman MS, Maggs DG, Shen LZ, Strobel SA, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemetic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care*. 2003 Mar;26(3):784-90.
27. Ratner RE, Want LL, Fineman MS, et al. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemetic and weight control in insulin-treated subjects with type 2 diabetes. *Diabetes Technol Ther*. 2002;4(1):51-61.
28. Hollander P, Ratner R, Fineman M, Strobel S, Shen L, Maggs D, et al. Addition of pramlintide to insulin therapy lowers A1C in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets. *Diabetes Obes Metab*. 2003 Nov;5(6):408-14.
29. Maggs D, Shen L, Strobel S, Brown D, Kolterman O, Weyer C. Effect of pramlintide on A1c and body weight in insulin treated African Americans and Hispanics with type 2 diabetes: a pooled post hoc analysis. *Metabolism*. 2003;52(12):1638-42.
30. Hollander P, Maggs D, Ruggles J, et al. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. *Obes Res*. 2004 Apr;12(4):661-8.
31. Riddle M, Pencek R, Charenkavanich S, et al. Randomized comparison of pramlintide or mealtime insulin added to basal insulin treatment for patients with type 2 diabetes. *Diabetes Care*. 2009;32:1577-82.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Biguanides
AHFS Class 682004
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Metformin is the only biguanide that is currently available and it is approved for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Insulin secretion remains unchanged; however, fasting insulin levels and day-long plasma insulin response may decrease.¹⁻⁶

The biguanides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Both the immediate-release and sustained-release tablets are available in a generic formulation. This class was last reviewed in February 2015.

Table 1. Biguanides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Metformin	Extended-release tablet, solution, tablet	Fortamet [®] *, Glucophage [®] *, Glucophage XR [®] *, Glumetza [®] *, Riomet [®]	metformin, metformin extended-release

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Biguanides

Clinical Guideline	Recommendation(s)
American Diabetes Association: Standards of Medical Care in Diabetes (2016) ⁷	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) \geq6.5%, or a fasting plasma glucose (FPG) \geq126 mg/dL, or a two-hour plasma glucose \geq200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose \geq200 mg/dL). <p>Prevention or delay of type 2 diabetes</p> <ul style="list-style-type: none"> An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to \geq150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. Metformin therapy for prevention of type 2 diabetes should be considered in

Clinical Guideline	Recommendation(s)
	<p>those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus.</p> <ul style="list-style-type: none"> • Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p><u>Glycemic goals in adults</u></p> <ul style="list-style-type: none"> • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p><u>Pharmacologic therapy for type 1 diabetes</u></p> <ul style="list-style-type: none"> • Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. • Most patients should use of insulin analogs to reduce hypoglycemia risk. • Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. <p><u>Pharmacologic therapy for type 2 diabetes</u></p> <ul style="list-style-type: none"> • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If the A_{1c} target is not achieved after approximately three months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • Pregestational Diabetes <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1c}

Clinical Guideline	Recommendation(s)
	<p><6.5%, to reduce the risk of congenital anomalies.</p> <ul style="list-style-type: none"> ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. <ul style="list-style-type: none"> ● Gestational Diabetes Mellitus <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. ● General Principles for Management of Diabetes in Pregnancy <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. ● Due to increased red blood cell turnover, A_{1c} is lower in normal pregnancy than in normal nonpregnant women. The A_{1c} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012 and 2015 Update)⁸</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> ● Glycemic targets and glucose-lowering therapies must be individualized. ● Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. ● Unless there are prevalent contraindications, metformin is the optimal first line drug. ● After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. ● Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. ● All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. ● Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> ● It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. ● Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. ● Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.

Clinical Guideline	Recommendation(s)												
	<ul style="list-style-type: none"> • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> • Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. • Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. • In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. • Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. <p>Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations</p> <table border="1" data-bbox="516 1717 1414 1902"> <thead> <tr> <th data-bbox="516 1717 704 1766">Initial Drug Monotherapy</th> <th data-bbox="704 1717 1414 1766">Metformin</th> </tr> </thead> <tbody> <tr> <td data-bbox="516 1766 704 1801">Efficacy (↓HbA_{1c})</td> <td data-bbox="704 1766 1414 1801">High</td> </tr> <tr> <td data-bbox="516 1801 704 1837">Hypoglycemia</td> <td data-bbox="704 1801 1414 1837">Low risk</td> </tr> <tr> <td data-bbox="516 1837 704 1873">Weight</td> <td data-bbox="704 1837 1414 1873">Neutral/loss</td> </tr> <tr> <td data-bbox="516 1873 704 1902">Side Effects</td> <td data-bbox="704 1873 1414 1902">Gastrointestinal/lactic acidosis</td> </tr> <tr> <td colspan="2" data-bbox="516 1902 1414 1902">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug</td> </tr> </tbody> </table>	Initial Drug Monotherapy	Metformin	Efficacy (↓HbA _{1c})	High	Hypoglycemia	Low risk	Weight	Neutral/loss	Side Effects	Gastrointestinal/lactic acidosis	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug	
Initial Drug Monotherapy	Metformin												
Efficacy (↓HbA _{1c})	High												
Hypoglycemia	Low risk												
Weight	Neutral/loss												
Side Effects	Gastrointestinal/lactic acidosis												
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug													

Clinical Guideline	Recommendation(s)						
	combination therapy (order not meant to denote any specific preference)						
	Two Drug Combinations	Metformin + sulfonylurea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)
	Efficacy (↓HbA _{1c})	High	High	Intermediate	Intermediate	High	Highest
	Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk
	Weight	Gain	Gain	Neutral	Loss	Loss	Gain
	Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia
	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)						
	Three Drug Combinations	Metformin + sulfonylurea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + SGLT2 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +
		TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonylurea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonylurea, TZD, SGLT2 inhibitor, or insulin	Sulfonylurea, TZD, DPP-4 inhibitor, or insulin	Sulfonylurea, TZD, or insulin	TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist
	If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents						
More Complex Insulin Strategies	Combination injectable therapy						
American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012) ⁹	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. 						
American Association of Clinical Endocrinologists/ American College Of Endocrinology: Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015) ¹⁰	<p><u>Antihyperglycemic pharmacotherapy for type 2 diabetes</u></p> <ul style="list-style-type: none"> The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement. Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. 						

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. • The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. • When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists: Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm 2016 (2016)¹¹</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} \leq6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • The therapeutic regimen should be as simple as possible to optimize adherence. <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a

Clinical Guideline	Recommendation(s)
	<p>majority of patients.</p> <ul style="list-style-type: none"> • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ Sodium glucose cotransporter 2 (SGLT-2) inhibitors. ○ DPP-4 inhibitors. ○ TZDs (use with caution). ○ Alpha-glucosidase inhibitors. • sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ DPP-4 inhibitors. ○ TZD. ○ Basal insulin. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Three-drug combination therapy</u></p> <ul style="list-style-type: none"> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors. ○ Colesevelam.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Insulin therapy algorithm</u></p> <ul style="list-style-type: none"> ● Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. ● Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. ● Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. ● Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <p><u>Basal insulin</u></p> <ul style="list-style-type: none"> ● Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. ● Titrate insulin dose every two to three days to reach glycemic goals. ● Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. ● Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p><u>Basal-bolus insulin regimens</u></p> <ul style="list-style-type: none"> ● Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. ● A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. ● Doses of insulin may be titrated every two to three days to reach glycemic goals. <p><u>Basal insulin and incretin therapy regimens</u></p> <ul style="list-style-type: none"> ● Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. ● The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last</p>	<p><u>Individualized care</u></p> <ul style="list-style-type: none"> ● Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity.

Clinical Guideline	Recommendation(s)
<p>updated July 2016)¹²⁻¹³</p>	<p>Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.</p> <ul style="list-style-type: none"> • Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p><u>HbA_{1c} targets</u></p> <ul style="list-style-type: none"> • Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. • For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. • In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> ○ reinforce advice about diet, lifestyle and adherence to drug treatment and ○ support the person to aim for an HbA_{1c} level of 7.0% and ○ intensify drug treatment. • Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> ○ who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy ○ for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job ○ for whom intensive management would not be appropriate, for example, people with significant comorbidities. • If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p><u>Drug treatment</u></p> <ul style="list-style-type: none"> • For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost • If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. • Initial drug treatment <ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m²: <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p>First intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. • Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes. <p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment. • If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. • Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had

Clinical Guideline	Recommendation(s)
	<p>a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in 6 months).</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment. • In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p><u>Insulin-based treatments</u></p> <ul style="list-style-type: none"> • When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional. • When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. • Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation. ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: <ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals. ○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes: <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. • Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). • Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)¹⁴</p>	<ul style="list-style-type: none"> • Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. • Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes (2012)¹⁵</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> • Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. • Match the timing of medication (including insulin) and meals. • Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. • Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals. • Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an

Clinical Guideline	Recommendation(s)
	<p>accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week.</p> <ul style="list-style-type: none"> • Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> • Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. • A lower HbA_{1c} target may be considered if it is easily and safely achieved. • A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> • Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. • Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. • First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. • Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. • Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering medications (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)¹⁶</p>	<ul style="list-style-type: none"> • Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations \geq250 mg/dL. ○ Whose HbA_{1c} is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
<p>National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November 2016)¹⁷</p>	<p>Education and information for children and young people with type 1 diabetes</p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. • Tailor the education programme to each child or young person with type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. <ul style="list-style-type: none"> ● Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. ● Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. ● Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. ● Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. ● Encourage children and young people with type 1 diabetes to wear or carry something that identifies them as having type 1 diabetes (e.g., a bracelet). ● Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. ● Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. ● Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations. ● Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p><u>Insulin therapy for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> ● While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. ● Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. • Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. • Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. • Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin infusion users. • Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. • Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin (0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%. • Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. • Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. • Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with type 1 diabetes a review of injection sites at each clinic visit. • Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. • If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily injections, continuous subcutaneous insulin infusion [CSII or insulin pump] therapy or once-, twice- or three-times daily mixed insulin injections). <p><u>Oral medicines for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood

Clinical Guideline	Recommendation(s)
	<p>glucose control is uncertain.</p> <ul style="list-style-type: none"> • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. <p><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. • Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. • Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. • Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain. <p><u>Education and information for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ HbA_{1c} monitoring and targets ○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control ○ the aims of metformin therapy and possible adverse effects ○ the complications of type 2 diabetes and how to prevent them. • Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every 2 years. • Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible government disability benefits. • Take particular care when communicating with and providing information to

Clinical Guideline	Recommendation(s)
	<p>children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English.</p> <p><u>Dietary management for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. • Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. • At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. • Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications. • Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. • Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. • At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI. • Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. • Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy. <p><u>Metformin</u></p> <ul style="list-style-type: none"> • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management (Published 2015; last updated July 2016)¹⁸</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> • Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. • Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target. • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles ○ total glycated hemoglobin estimation (if abnormal hemoglobins). • Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. • Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of

Clinical Guideline	Recommendation(s)
	<p>hypoglycemia.</p> <ul style="list-style-type: none"> • Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p><u>Self-monitoring of blood glucose</u></p> <ul style="list-style-type: none"> • Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least four times a day, including before each meal and before bed. • Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). • Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia. • Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. • Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy) • Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking. <p><u>Continuous glucose monitoring</u></p> <ul style="list-style-type: none"> • Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. • Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause. ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level $\geq 9\%$) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in HbA_{1c} of 2.5% or more. • For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy.

Clinical Guideline	Recommendation(s)
	<p><u>Insulin regimens</u></p> <ul style="list-style-type: none"> • Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. • Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only). <p><u>Long-acting insulin</u></p> <ul style="list-style-type: none"> • Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. • Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul style="list-style-type: none"> ○ an existing insulin regimen being used by the person that is achieving their agreed targets ○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. • Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p><u>Rapid-acting insulin</u></p> <ul style="list-style-type: none"> • Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. • Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. • If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. <p><u>Mixed insulin</u></p> <ul style="list-style-type: none"> • Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. • Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p><u>Optimizing insulin therapy</u></p> <ul style="list-style-type: none"> • For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously optimized insulin regimen, the following should be considered: <ul style="list-style-type: none"> ○ injection technique ○ injection sites ○ self-monitoring skills ○ knowledge and self-management skills ○ nature of lifestyle ○ psychological and psychosocial difficulties ○ possible organic causes such as gastroparesis. • Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. <p><u>Adjuncts</u></p> <ul style="list-style-type: none"> • Consider adding metformin to insulin therapy if an adult with type 1 diabetes

Clinical Guideline	Recommendation(s)
	<p>and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose.</p> <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> • Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. • Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. • Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. • After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. • Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. • Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. • Check injection site condition at least annually and if new problems with blood glucose control occur.
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)¹⁹</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> • Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. • If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <p><u>Glycemic control goals</u></p> <ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and

Clinical Guideline	Recommendation(s)
	<p>HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development.</p> <ul style="list-style-type: none"> • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p> <ul style="list-style-type: none"> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the biguanides are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Biguanides¹⁻⁴

Indication	Metformin
Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus	✓

IV. Pharmacokinetics

The pharmacokinetic parameters of the biguanides are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Biguanides⁵

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Excretion (%)	Half-Life (hours)
Metformin	50 to 60 [†]	Negligible (% not reported)	Renal (90)	1.5 to 6.2 (plasma) 17.6 (blood)

[†]Immediate-release formulations

V. Drug Interactions

Significant drug interactions with the biguanides are listed in Table 5.

Table 5. Significant Drug Interactions with the Biguanides⁵

Generic Name(s)	Interaction	Mechanism
Metformin	Iodinated contrast materials, parenteral	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis.

VI. Adverse Drug Events

The most common adverse drug events reported with the biguanides are listed in Table 6. The boxed warnings for metformin-containing products are listed in Tables 7 and 8.

Table 6. Adverse Drug Events (%) Reported with the Biguanides¹⁻⁴

Adverse Events	Metformin	
	Immediate-Release Formulations	Metformin Sustained-Release Formulations
Cardiovascular		
Chest discomfort	-	1 to 5*
Hypertension	-	1 to 5*
Palpitations	1 to 5	-
Central Nervous System		
Asthenia	9.2	1 to 5*
Dizziness	-	1 to 5
Headache	5.7	4.7 to 5
Lightheadedness	1 to 5	-
Gastrointestinal		
Abdominal discomfort	6.4	-
Abdominal pain	-	1 to 5
Abnormal stools	1 to 5	1 to 5*
Constipation	-	1 to 5
Diarrhea	53.2	9.6 to 16.7
Distention abdomen	-	1 to 5
Dyspepsia/heartburn	-	1 to 5
Flatulence	12.1	1 to 5
Indigestion	7.1	-
Loose stools	-	1 to 5*
Nausea/vomiting	25.5	6.5 to 8.5
Respiratory		
Dyspnea	1 to 5	-
Rhinitis	-	4.2

Adverse Events	Metformin Immediate-Release Formulations	Metformin Sustained-Release Formulations
Upper respiratory infection	-	1 to 5
Miscellaneous		
Accidental injury	-	5.6 to 7.3
Contusion	-	1 to 5*
Ear pain	-	1 to 5*
Flu syndrome	1 to 5	1 to 5*
Hypoglycemia	1 to 5	13.7*
Increased sweating	1 to 5	-
Infection	20.9	20.5, 1 to 5*
Myalgia	1 to 5	1 to 5*
Nail disorder	1 to 5	-
Rash	1 to 5	-
Seasonal allergy	-	1 to 5*
Taste disorder	1 to 5	1 to 5
Toothache	-	1 to 5*
Tonsillitis	-	1 to 5*
Tremor	-	1 to 5*

- Event not reported

*Reported with Glumetza®

Table 7. Boxed Warning for Fortamet®, Glucophage®, Glucophage XR®, and Riomet® (metformin)^{1,2,4}

WARNING
<p>Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure. The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated,</p>

WARNING
<p>blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/minute under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.</p>

Table 8. Boxed Warning for Glumetza® (metformin)³

WARNING
<p>Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, Glumetza®, should be discontinued and the patient hospitalized immediately.</p>

VII. Dosing and Administration

The usual dosing regimens for the biguanides are listed in Table 9.

Table 9. Usual Dosing Regimens for the Biguanides¹⁻⁴

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Metformin	<p><u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u></p> <p>Oral solution, tablet: initial, 500 mg BID or 850 mg QD; maintenance, 2,000 mg/day administered in divided doses; maximum, 2,550 mg/day</p> <p>Sustained-release tablet (Fortamet®): initial, 500 or 1,000 mg QD; maximum, 2,500 mg/day</p> <p>Sustained-release tablet (Glucophage XR®, Glumetza®): initial, 500 mg QD; maximum, 2,000 mg QD</p>	<p><u>Adjunct to diet and exercise to improve glycemic control in children 10 to 16 years of age with type 2 diabetes mellitus:</u></p> <p>Oral solution, tablet: initial, 500 mg BID; maximum, 2,000 mg/day</p>	<p>Oral solution (Riomet®): 500 mg/5 mL</p> <p>Sustained-release tablet: 500 mg (Fortamet®, Glucophage XR®, Glumetza®) 750 mg (Glucophage XR®) 1,000 mg (Fortamet®, Glumetza®)</p> <p>Tablet (Glucophage®): 500 mg 850 mg 1,000 mg</p>

BID=twice daily, QD=once daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the biguanides are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Biguanides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
Jones et al. ²⁰ (2002) Metformin 1,000 to 2,000 mg daily vs placebo	DB, MC, PC, RCT Patients 8 to 16 years of age with type 2 diabetes, FPG 7.0 to 13.3 mmol/L, HbA _{1c} ≥7.0%, stimulated C-peptide ≥0.5 nmol/L, and BMI >50 th percentile for age	N=82 16 weeks	Primary: Change in baseline FPG Secondary: Change in baseline HbA _{1c} , body weight, height, BMI, lipid stimulated C-peptide levels	Primary: Adjusted mean change from baseline in FPG for metformin was -2.4 mmol/L compared to 1.2 mmol/L for placebo (P<0.001). Secondary: Mean HbA _{1c} levels, adjusted for baseline levels, were significantly lower for metformin compared to placebo (7.5 vs 8.6%, respectively; P<0.001). Mean TC decreased from baseline in the metformin group (-0.25 mmol/L [-9.7 mg/dL]) compared to a slight increase in the placebo group (0.01 mmol/L [0.7 mg/dL]; P=0.043). Mean LDL-C decreased more with metformin (-0.11 mmol/L [-4.2 mg/dL] vs -0.10 mmol/L [4 mg/dL]; P=0.053). No between-group differences were seen in the mean adjusted changes in HDL-C or TGs. Mean weight changes and mean BMI changes from baseline were comparable between the treatment groups. There was no between-group difference seen in the adjusted mean stimulated C-peptide change from baseline (-0.2 nmol/L for both groups [-0.7 vs -0.6 ng/mL]). The most common reported adverse events were abdominal pain, diarrhea, nausea/vomiting, and headache. Patients receiving metformin experienced more abdominal pain (25%) vs placebo (12%) and more nausea/vomiting (17%) vs placebo (10%).
Bhansali et al. ²¹ (2005)	OL	N=40	Primary: Changes in four-	Primary: Mean fasting glucose was <120 mg/dL in 80, 63, 73, and 90% of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Month 1: After a lead-in period of 3 months on their usual metformin IR regimen, patients were evaluated (visit 0, baseline) and started on a specific brand of metformin IR at their usual dose, 1,000 to 2,000 mg daily, and continued on this regimen for 1 month until visit 1.</p> <p>Month 2: patients were evaluated (visit 1) and changed over to metformin ER as a single dose at dinner, at a dose 500 mg less than the baseline dose of metformin IR; they continued on this regimen for 1 month</p> <p>Month 3: patients were evaluated (visit 2) and changed over</p>	<p>Patients ≥ 40 years of age with type 2 diabetes, BMI ≥ 20 kg/m², HbA_{1c} $\leq 8.5\%$, and a fasting capillary glucose ≤ 120 mg/dL who had achieved moderate or good glycemic control with metformin IR alone or in combination with other antihyperglycemic agents</p>	<p>7 months (3 month lead-in and 4 month observation)</p>	<p>point glucose profile at each visit and in HbA_{1c} at the end of the study period, changes in weight and lipid profiles, compliance was assessed by reviewing the tablet counts conducted at each study visit and patients were asked to confirm their compliance with therapy at each visit (acceptable compliance was defined as $>80\%$ of expected study drug consumption)</p> <p>Secondary: Not reported</p>	<p>at visits one, two, three, and four, respectively; these differences were not significant.</p> <p>Mean post-breakfast glucose was 149, 165 (P=0.009), 158 (P=0.159), and 159 mg/dL (P=0.111) at visits one, two, three, and four, respectively (P values are when compared to visit one).</p> <p>Mean post-lunch glucose was 130, 154 (P=0.003), 151 (P=0.012), and 138 mg/dL (P=0.076) at visits one, two, three, and four, respectively (P values are when compared to visit one).</p> <p>Mean post-dinner glucose was 138, 161 (P=0.020), 138 (P=0.967), and 128 mg/dL (P=0.264) at visits one, two, three, and four, respectively (P values are when compared to visit one).</p> <p>Mean PPG was 139, 160 (P=0.001), 149 (P=0.065), and 142 mg/dL (P=0.289) at visits one, two, three, and four, respectively (P values are when compared to visit one).</p> <p>Mean HbA_{1c} after three months of metformin ER (visit 4) was 6.3% compared to baseline HbA_{1c} of 6.9% with metformin IR (P=0.008). No other HbA_{1c} values were reported. Patients switched over to the ER formulation, once re-established at doses equivalent to their baseline metformin IR doses, and achieved glycemic control comparable to baseline levels.</p> <p>Mean weight at the end of three months of metformin ER (visit four) was 68.7\pm10.2 kg as compared to 69.6\pm10.8 kg at baseline (P=0.020).</p> <p>Lipid profile after three months of metformin XR was the following: mean TC (182\pm29 mg/dL), LDL-C (113\pm26 g/dL), HDL-C (45\pm8 mg/dL), and TG (119\pm55 mg/dL). These were not statistically significant from baseline.</p> <p>Two patients complained of diarrhea and one had loss of appetite and complained of diarrhea during the new metformin XR regimen.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>to metformin XR 1,000 to 2,000 mg daily at bedtime, keeping the dose the same as their baseline metformin IR dose; they continued on this regimen for 1 month</p> <p>Month 4: patients were evaluated (visit 3) and changed over to metformin XR 1,000 to 2,000 mg daily in two divided doses keeping the dose the same as baseline metformin IR dose; they continued on this regimen for 1 month</p> <p>Patients were evaluated at the end of the study (visit 4).</p>				<p>Secondary: Not reported</p>
<p>Blonde et al.²² (2004)</p> <p>Metformin XR 500 to 2,500 mg daily</p>	<p>MC, RETRO</p> <p>Patients ≥ 17 years of age with type 2 diabetes who were started on</p>	<p>N=468</p> <p>1 year</p>	<p>Primary: Gastrointestinal tolerability and frequency of diarrhea for metformin XR</p>	<p>Primary: Overall metformin XR vs metformin IR cohorts: The frequency of gastrointestinal events was similar between metformin XR and metformin IR (11.94 vs 11.39%, respectively; P=0.86).</p> <p>The RR of any gastrointestinal adverse event for metformin XR compared</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs metformin IR 500 to 2,500 mg daily</p>	<p>metformin XR (Glucophage XR®), or switched from metformin IR or another oral antidiabetic agent to metformin XR within the previous 2 years</p>		<p>compared to metformin IR during the first year of treatment</p> <p>Secondary: Not reported</p>	<p>to metformin IR was 1.05 (95% CI, 0.62 to 1.78).</p> <p>The percentages of patients with individual gastrointestinal adverse events in the metformin XR and metformin IR groups, respectively were as follows: diarrhea (6.77 vs 7.59%), nausea (2.26 vs 3.80%), dyspepsia (1.61 vs 1.27%), abdominal pain (1.61 vs 0.63%), constipation (0.97 vs 0.63%), vomiting (0.65 vs 0.63%), abdominal distention (0.32 vs 0.00%), fecal abnormality (0.32 vs 0.63%), blood in stools (0.00 vs 0.63%), and flatulence (0.00 vs 0.63%).</p> <p>Patients switched from metformin IR to metformin XR: Significantly more patients experienced a gastrointestinal adverse event during the first year of treatment with metformin IR (26.34%, 54/205; P=0.006) than after switching to metformin XR (11.71%, 24/205). The mean daily dose of metformin XR was 1,184 mg (range, 500 to 2,500 mg) during the first year of therapy and 1,047 mg (range, 500 to 2,550 mg) for the metformin IR groups.</p> <p>A significantly higher percentage of patients reported diarrhea (18.05%, 37/205) while taking metformin IR than after switching to metformin XR (8.29%, 17/205; P=0.0084).</p> <p>More patients reported nausea (2.93%), dyspepsia (3.41%), abdominal distention (2.44%), and flatulence (2.44%) while taking the metformin IR than after switching to metformin XR (1.95, 1.46, 0.49, and 0.0%, respectively); however, the differences were not significant.</p> <p>Patients new to metformin XR vs metformin IR: A greater percent of patients reported a gastrointestinal adverse event during the first year of treatment with metformin IR (19.83%, 72/363) than during the first year of therapy with metformin XR (9.23%, 6/65; P=0.0414).</p> <p>A greater percent of patients taking metformin IR reported diarrhea (13.5%, 49/363) as compared to the metformin XR group (3.08%, 2/65; P=0.0169).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Fujioka et al.²³ (2003)</p> <p>Metformin XR (Glucophage XR®) 1,000 mg QD with the evening meal</p> <p>vs</p> <p>metformin XR 1,000 mg QD with the evening meal for 1 week, then increased to 1,500 mg QD</p> <p>vs</p> <p>continued metformin IR 500 mg BID</p> <p>Note: after 12 weeks, the daily dose of metformin could be increased by 500 mg in any group if HbA_{1c} was ≥8.0% at that time.</p>	<p>DB, MC, PG, RCT</p> <p>Patients to 27 to 77 years of age with type 2 diabetes for >2 months to <10 years, HbA_{1c} ≤8.5%, FPG ≤200 mg/dL, and receiving metformin IR 500 mg BID for ≥8 weeks</p>	<p>N=217</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c} from baseline to week 12 with the switch from metformin IR to metformin XR</p> <p>Secondary: Change in baseline HbA_{1c} to week 24, changes in FPG, mean daily blood glucose concentrations, fructosamine, serum insulin levels, lipid levels, body weight, safety</p>	<p>Secondary: Not reported</p> <p>Primary: Mean changes from baseline in HbA_{1c} values at week 12 were small and similar in the three treatment groups. At week 12, the mean change from baseline was 0.15% for metformin IR, 0.23% for metformin XR 1,000 mg, and 0.04% for metformin XR 1,500 mg.</p> <p>Secondary: The corresponding changes in HbA_{1c} values at week 24 were small and similar among the three treatment groups: 0.06% for metformin IR, 0.25% for metformin XR 1,000 mg, and 0.14% for metformin XR 1,500 mg. The distribution of HbA_{1c} values in the specified categories (<7.0, 7.0 to <8.0, and ≥8.0%, respectively) was not significant between the groups during the study.</p> <p>Mean FPG concentrations had also increased in all three treatment groups at week 12 and 24. The mean increases were smaller in the metformin XR groups compared to the metformin IR group.</p> <p>No clinically relevant significant changes from baseline were seen in HDL-C or TC levels in any treatment group. LDL-C decreased in all treatment groups, with a mean change of -4 mg/dL in the metformin IR group (95% CI, -9 to 1), and -6 mg/dL in both XR groups (1,000 mg XR, 95% CI, -11 to -1; 1,500 mg XR, 95% CI, -12 to 0). There were small increases from baseline in TG levels in patients receiving metformin IR (mean change, 1 mg/dL; 95% CI, -14 to 17). There were significant increases in TGs in patients receiving metformin XR. Patients in the 1,000 mg group had an increase of 34 mg/dL (95% CI, 15 to 53) and patients in the 1,500 mg group had an increase of 42 mg/dL (95% CI, 6 to 78).</p> <p>Mean daily blood glucose concentration, fructosamine, serum insulin levels, and body weight showed similar changes in each group.</p> <p>Twenty-five percent of patients in the metformin IR group, 29% of patients in the metformin XR 1,000 mg group, and 34% of patients in the metformin XR 1,500 mg group experienced adverse drug events</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>(occurring in $\geq 3\%$ of patients). Diarrhea, flatulence, abdominal pain, and nausea/vomiting were the most common adverse events reported among all groups combined. Three percent of metformin IR, 5% of metformin XR 1,000 mg, and 15% of metformin 1,500 mg patients experienced diarrhea. Flatulence was reported in 1% of metformin IR patients, 4% of metformin XR 1,000 mg patients, and 3% of metformin XR 1,500 mg patients. Abdominal pain was reported in 1% of metformin IR patients and metformin XR 1,500 mg patients and in 4% of metformin XR 1,000 mg patients. Nausea/vomiting were reported in 4% of metformin IR patients and 3% in both metformin XR groups. Headache was reported in 4% of metformin IR and metformin XR 1,000 mg patients. Dyspepsia/heartburn was reported in 6% of metformin IR and 3% of metformin XR 1,000 mg patients. The study was not statistically powered to detect differences in tolerability between the groups.</p>
<p>Schwartz et al.²⁴ (2006)</p> <p>Metformin XR 1,500 mg QD</p> <p>vs</p> <p>metformin XR 1,500 mg daily in 2 divided doses</p> <p>vs</p> <p>metformin XR 2,000 mg QD</p> <p>vs</p> <p>metformin IR 1,500 mg daily in 2 divided doses</p>	<p>AC, DB, MC, RCT</p> <p>Patients 18 to 79 years of age with type 2 diabetes, HbA_{1c} 7.0 to 12.0% (drug-naïve patients) or 6.5 to 10.0% (prior drug therapy patients), FPG 120 to 400 mg/dL (drug-naïve patients) or 120 to 250 mg/dL (prior drug therapy patients), C-peptide levels >1 ng/mL, and BMI 22 to 50 kg/m²</p>	<p>N=750</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, fructosamine, TC, HDL-C, LDL-C, and TG</p>	<p>Primary: Reductions in mean HbA_{1c} were significant by week 12 for all groups, continued to decline until week 20, and were maintained for the duration of the study. The change from baseline was significant for each group (P<0.001).</p> <p>Mean changes in HbA_{1c} from baseline to end point in all metformin XR groups were similar to the metformin IR groups. Mean changes in HbA_{1c} from baseline to end point in the two groups given 1,500 mg metformin XR (-0.73% and -0.74%) were not significantly different from the change in the metformin IR group (-0.70%), whereas the 2,000 mg metformin XR group showed a greater decrease in HbA_{1c} levels (-1.06%).</p> <p>Secondary: Reductions in mean FPG were significant in all groups by the end of week one, declined until week eight, and these levels were maintained until the end of the study. The change from baseline was significant for each group (P<0.001). The mean changes from baseline to end point within each of the metformin XR groups were comparable with or greater than that in the metformin IR group (P=0.051 for overall comparison among groups).</p> <p>Mean fructosamine levels decreased from baseline within all groups. There was a significant difference among groups for fructosamine levels at</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>the end point, with the lowest level observed with the 2,000 mg once daily metformin XR group.</p> <p>TC, LDL-C, and HDL-C levels were similar at baseline and end point with all treatment groups, except for differences with treatment groups for final LDL-C (P=0.015) and TG (P=0.030). The lowest mean concentrations for LDL-C and TG occurred with 2,000 mg QD metformin XR and metformin IR, respectively.</p> <p>Overall incidence of gastrointestinal adverse events was low and comparable among treatment groups during the first week of treatment. There was a higher incidence of nausea in the metformin IR group than in the metformin XR groups (P=0.05) during the first week.</p> <p>Overall incidence of adverse events considered possibly or probably related to the study drug was similar for all groups. The only events reported for >5% of patients in any group during the entire study were gastrointestinal (diarrhea, nausea, dyspepsia, upper abdominal pain).</p>
<p>Pavo et al.²⁵ (2003)</p> <p>Metformin 850 to 2,550 mg daily</p> <p>vs</p> <p>pioglitazone 30 to 45 mg daily</p>	<p>DB, MC, RCT</p> <p>Recently diagnosed (<12 months) type 2 diabetic patients ≥40 years of age, HbA_{1c} of 7.5 to 11.0%, and naïve to oral antihyperglycemic medications</p>	<p>N=205</p> <p>32 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Changes in FPG, fasting serum insulin, and insulin sensitivity</p>	<p>Primary: Each treatment group had a significant reduction in HbA_{1c} from baseline (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.280).</p> <p>Secondary: Each treatment group had a significant reduction in FPG (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.620).</p> <p>Pioglitazone reduced fasting serum insulin significantly (P<0.0001). The change in fasting serum insulin was not significant for metformin (P=0.803).</p> <p>Pioglitazone was significantly more effective than metformin in improving indicators of insulin sensitivity, as determined by reduction of fasting serum insulin (P=0.003) and by analysis of HOMA-S (P=0.002).</p>
<p>Cryer et al.²⁶ (2005)</p>	<p>MC, OL, PG, RCT</p>	<p>N=8,732</p>	<p>Primary: Incidence of</p>	<p>Primary: Serious adverse reactions were reported in 10.3% (95% CI, 9.6 to 11.1) of</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Metformin 500 mg BID to 2,500 mg daily in 3 divided doses</p> <p>vs</p> <p>usual care</p>	<p>Type 2 diabetic patients ≥ 18 years of age with glycemia inadequately controlled with diet or a sulfonylurea</p>	<p>1 year</p>	<p>serious adverse events, death, hospitalization</p> <p>Secondary: Plasma lactate levels after one year of treatment in a substudy</p>	<p>patients in the metformin group and by 11.0% (95% CI, 9.5 to 12.7) of patients in the usual care group ($P=0.43$), with similar pattern of serious adverse events between groups according to body system. Serious cardiovascular adverse events were the most common, which included coronary artery disease (1.0 vs 1.1%) for metformin vs usual care, respectively, chest pain (0.7 vs 1.0%), congestive heart failure (0.7 vs 0.6%), MI (0.7 vs 0.7%), and cerebrovascular accident (0.4 vs 0.7%). There was not an excess of serious adverse events observed in the metformin group in all patients regardless of age.</p> <p>The incidence of all-cause hospitalization, hospitalization for metabolic causes (other than lactic acidosis), and all-cause mortality did not differ between metformin and usual care in the overall population ($P=0.229$, $P=1.0$, $P=0.596$, respectively) or in patients ≥ 65 years old ($P=0.178$, $P=1.0$, $P=0.878$, respectively), or in younger patients ($P=0.945$, $P=0.835$, $P=0.21$, respectively). There were no patients that were hospitalized or that died from lactic acidosis.</p> <p>Secondary: Mean plasma lactate was 1.7 ± 0.6 mmol/L in the metformin group and 1.6 ± 0.6 mmol/L in the usual care group after 12 months of therapy ($P=0.137$). Plasma lactate >3 mmol/L occurred in 4% of metformin patients and 1% in the usual care group. There was no significant difference between the groups.</p>
<p>Gottschalk et al.²⁷ (2007)</p> <p>Metformin 500 to 1,000 mg BID</p> <p>vs</p> <p>glimepiride 1 to 8 mg QD</p>	<p>AC, MC, PG, SB, RCT</p> <p>Pediatric subjects 8 to 17 years of age with type 2 diabetes ($HbA_{1c} >7.1$ and $<12.0\%$) with inadequate control despite treatment with either diet and exercise alone for at least 2 weeks prior</p>	<p>N=285</p> <p>24 weeks</p>	<p>Primary: Mean change in HbA_{1c} from baseline to week 24</p> <p>Secondary: Mean change in HbA_{1c} from baseline to week 12, proportion of patients achieving an $HbA_{1c} <7.0\%$ at</p>	<p>Primary: Significant reductions from baseline HbA_{1c} were seen in both the glimepiride (-0.54%; $P=0.001$) and metformin (-0.71%; $P=0.0002$) groups. No significant differences were observed between groups in reductions in HbA_{1c}.</p> <p>Secondary: Significant reductions in the adjusted mean change from baseline HbA_{1c} to week 12 were -0.69 and -0.76% in patients receiving glimepiride and metformin, respectively ($P<0.05$).</p> <p>A total of 42.4 and 48.1% of patients in the glimepiride and metformin groups, respectively, achieved $HbA_{1c} <7.0\%$ at week 24 ($P=0.347$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	to randomization or diet and exercise combined with 3 months of ongoing or previous oral antidiabetic monotherapy		week 24, mean change in fasting self-monitoring of blood glucose from baseline to weeks four, eight, 12, 18, and 24, mean changes in serum lipid concentrations from baseline to week 24 and changes in BMI, safety, adverse events, hypoglycemic episodes and vital signs	<p>Significant reductions were seen in fasting self-monitoring of blood glucose levels from baseline to weeks 18 and 24 in patients receiving metformin (P<0.05) but no similar reductions were reported in the glimepiride group.</p> <p>There were no significant differences between the glimepiride and metformin groups in the mean change from baseline in any of the serum lipid concentrations.</p> <p>Significant between-group differences were observed in the mean change from baseline BMI to week 24. Values were 0.26 and 0.33 kg/m² in patients receiving glimepiride and metformin, respectively (P=0.003).</p> <p>No deaths occurred during the study. The proportions of patients experiencing ≥1 adverse event were comparable between both treatment groups, with the most common adverse events being hyperglycemia, upper abdominal pain, diarrhea, nausea and headache. Two patients experienced serious adverse events that were considered possibly related to treatment: one patient in the glimepiride group had hyperglycemia, diabetic ketoacidosis and increased serum osmolarity and one patient in the metformin group had a non-hypoglycemic convulsion.</p> <p>The incidence of clinically relevant hypoglycemia was similar in both groups (P=0.554).</p> <p>No clinically significant differences in vital signs were seen between treatment groups.</p>
Hong et al. ²⁸ (2013) SPREAD-DIMCAD Metformin 0.75 to 1.5 grams daily vs	DB, MC, PC, RCT Patients 80 years of age or below with coronary artery disease (CAD) and type 2 diabetes	N=304 3 years	Primary: Composite of recurrent cardiovascular events (myocardial infarction [MI], nonfatal stroke, arterial revascularization,	Primary: A total of 103 composite primary end points occurred in 91 during the whole study period: 60 events in the glipizide group (14 deaths from any causes [including 11 deaths from cardiovascular events and 3 from sudden death; autopsies were not performed to confirm the 3 patients' precise causes of death], 6 nonfatal myocardial infarctions, 15 nonfatal strokes, and 25 arterial revascularizations), as compared with 43 events in the metformin group (7 deaths from any causes [all were deaths from cardiovascular events], 5 nonfatal myocardial infarctions, 10 nonfatal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glipizide 15 to 30 mg daily			<p>death)</p> <p>Secondary: New or worsening angina, new or worsening heart failure, new critical cardiac arrhythmia, and new peripheral vascular events.</p>	<p>strokes, and 21 arterial revascularizations). As compared with the patients treated with glipizide, the HR for the composite cardiovascular events for metformin treatment was 0.54 (95% CI 0.30 to 0.90; P=0.026) after adjustment for the duration of diabetes, duration of CAD, age, sex, and smoking history at baseline. No significant difference in the mortality rate between the two groups was found (P=0.55).</p> <p>Secondary: During the study drug administration, the following secondary end points occurred:</p> <ul style="list-style-type: none"> • new or worsening heart failure: 10 (6.8%) patients in the glipizide group and 9 (5.8%) patients in the metformin group (adjusted HR, 0.82; 95% CI, 0.31 to 2.13; P=0.677) • new critical cardiac arrhythmia: 27 (18.2%) patients in the glipizide group and 30 (19.2%) patients in the metformin group (HR, 1.01; CI, 0.60 to 1.72; P=0.958) • new or worsening angina: 71 (48%) patients in the glipizide group and 77 (49.4%) patients in the metformin group (HR, 1.07; CI, 0.77 to 1.48; P=0.696) • new peripheral vascular events: 6 (4.1%) patients in the glipizide group and 1 (0.6%) patient in the metformin group (HR, 0.13; CI, 0.02 to 1.08; P=0.059) <p>Furthermore, the two groups did not differ significantly with respect to the number of patients who reported one or more hypoglycemic attacks during study drug administration.</p>
<p>Lund et al.²⁹ (2008)</p> <p>Repaglinide 2 mg TID for 4 months</p> <p>vs</p> <p>metformin 1,000 mg BID for 4 months</p>	<p>DD, XO</p> <p>Non-obese (BMI ≤27 kg/m²), insulin-naïve patients with type 2 diabetes mellitus</p>	<p>N=96</p> <p>8 months with 1 month washout</p>	<p>Primary: Cardiovascular disease biomarkers and metabolic regulation</p> <p>Secondary: Not reported</p>	<p>Primary: Levels of TNF-α, plasminogen activator inhibitor-1 antigen, tissue-type plasminogen activator antigen, von Willebrand factor, soluble intercellular adhesion molecule-1 and soluble E-selectin were significantly lower during metformin treatment compared with repaglinide treatments.</p> <p>Amadori albumin and heart rate were higher during metformin compared with repaglinide.</p> <p>Both treatment groups experienced similar levels of interleukin-6, fibrinogen, soluble vascular cell adhesion molecule-1, asymmetric dimethylarginine and advanced glycation end products as well as glycemic</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				levels and 24 hour BP. Secondary: Not reported
Lund et al. ³⁰ (2008) Repaglinide 2 mg TID for 4 months vs metformin 1,000 mg BID for 4 months	DD, XO Non-obese (BMI ≤27 kg/m ²), insulin- naïve patients with type 2 diabetes mellitus	N=192 8 months with 1 month washout	Primary: Postprandial metabolism with blood sampling 0 to six hours postprandially Secondary: Not reported	Primary: Both treatment groups equally changed fasting levels and total AUC for plasma glucose, TGs and FFA. The metformin treatment group obtained lower fasting levels and AUC of TC, LDL-C, and non-HDL-C and serum insulin compared with repaglinide. After adjusting for fasting levels, AUC differences still remained significant. Secondary: Not reported
Fang et al. ³¹ (2014) Repaglinide vs metformin	OL, PG, RCT Chinese drug-naïve patients aged 20 to 90 years with newly diagnosed type 2 diabetes mellitus with a BMI of 18.5 to 30 kg/m ² and with an HbA _{1c} <10.0%	N=60 15 weeks	Primary: Change in HbA _{1c} from baseline Secondary: Changes in glycemic variability, insulin sensitivity, β-cell function	Primary: At week 15, mean changes in HbA _{1c} from baseline were -1.8±1.5% in the repaglinide group (P<0.01) and -1.6±1.5% in the metformin group (P<0.01). No significant difference was found with regard to change in HbA _{1c} level between the two groups (P=0.739). Secondary: No significant differences in secondary outcomes were found between the groups.
Sullivan et al. ³² (2011) FIELD Metformin vs sulfonylurea	PRO Patients with type 2 diabetes	N=6,005 5 years	Primary: Cardiovascular disease outcomes Secondary: Hypoglycemic therapy	Primary: Patients receiving monotherapy with either metformin or a sulfonylurea appeared to be at greater risk of cardiovascular disease compared to those on diet alone, but results were only significant for the sulfonylurea group, ranging from 42% higher risk of coronary revascularization to a doubled risk of coronary heart disease death. However, adjustment for the duration and intensity of diabetes and the severity of other cardiovascular risk factors abolished the significance of this effect. Total revascularization and total mortality were significantly higher in the sulfonylurea group compared to the metformin group, but all differences became non-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs diet alone				<p>significant on adjustment.</p> <p>Secondary: Use of oral hypoglycemic agents increased progressively as the trial proceeded. Over five years, treatment with diet alone decreased from 31 to 15%, and dual therapy with metformin plus a sulfonylurea increased from 29 to 36%. Insulin therapy was introduced at a rate of 4% per year. Metformin monotherapy declined from 21 to 18% but the sulfonylurea monotherapy rate declined from 20 to 12%. Patients on sulfonylurea monotherapy were more likely to progress to dual therapy.</p>
<p>Kahn et al.³³ (2006)</p> <p>Metformin 500 to 1,000 mg BID</p> <p>vs</p> <p>rosiglitazone 4 mg QD to 4 mg BID</p> <p>vs</p> <p>glyburide 2.5 to 7.5 mg BID</p>	<p>DB, MC, RCT</p> <p>Recently diagnosed (within 3 years) type 2 diabetic patients between 30 to 75 years of age who had not received previous pharmacologic treatment, with FPG levels ranging from 126 to 180 mg/dL while their only treatment was lifestyle management</p>	<p>N=4,360</p> <p>4 to 6 years (median treatment durations 3.3 years for glyburide and 4 years for rosiglitazone and metformin)</p>	<p>Primary: Time from randomization to treatment failure (defined as FPG >180 mg/dL on consecutive testing after at least six weeks of treatment at the maximum tolerated dose)</p> <p>Secondary: Time from randomization to a confirmed FPG >140 mg/dL after at least six weeks of treatment at the maximum tolerated dose (for patients who entered the study with FPG ≤140 mg/dL); FPG, HbA_{1c}, weight, measures of insulin</p>	<p>Primary: At five years, 15% of patients receiving rosiglitazone, 21% of those on metformin, and 34% of those on glyburide had failed monotherapy. This represents a risk reduction of 32% for rosiglitazone as compared with metformin and 63% for rosiglitazone as compared with glyburide (P<0.001 for both comparisons).</p> <p>Secondary: Progression to a confirmed FPG ≥140 mg/dL was seen in 79 of 511 patients in the rosiglitazone group as compared with 127 of 520 patients in the metformin group (P=0.002) and 160 of 480 patients in the glyburide group (P<0.001).</p> <p>At the four-year evaluation, 40% of the patients in the rosiglitazone group achieved an HbA_{1c} <7.0% compared with 36% of the patients in the metformin group (P=0.03) and 26% of the patients in the glyburide group (P<0.001).</p> <p>The annual rate of β-cell function decline after six months was greatest in the glyburide group (6.1% decreased), followed by the metformin group (3.1% decreased) and rosiglitazone group (2.0% decreased) (P<0.001 for rosiglitazone vs glyburide and P=0.02 for rosiglitazone vs metformin).</p> <p>Over a period of five years, the mean weight increased in the rosiglitazone group but decreased in the metformin group. In the glyburide group, weight gain occurred in the first year then remained stable.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			sensitivity, β -cell function, and adverse events	Treatment with glyburide was associated with lower risk of cardiovascular events (including congestive heart failure) than was seen in the rosiglitazone and metformin groups ($P < 0.05$). Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide, but fewer gastrointestinal events were reported with rosiglitazone compared to metformin and fewer hypoglycemic events were seen with rosiglitazone compared to with glyburide ($P < 0.001$ for all comparisons).
<p>Aschner et al.³⁴ (2010)</p> <p>Metformin 1,000 mg BID</p> <p>vs</p> <p>sitagliptin 100 mg QD</p>	<p>AC, DB, RCT</p> <p>Patients 18 to 78 years of age with type 2 diabetes mellitus who were treatment naïve with an HbA_{1c} of 6.5 to 9.0%</p>	<p>N=1,050</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Proportions of patients with HbA_{1c} <7.0% or <6.5%, change in FPG, fasting serum insulin, fasting serum proinsulin, and lipid parameters</p>	<p>Primary:</p> <p>In the per protocol population, the change in HbA_{1c} (least squares mean) from baseline at week 24 was -0.43% in the sitagliptin group and -0.57% in the metformin group (difference, 0.14%; 95% CI, 0.06 to 0.21), which demonstrated the non-inferiority of sitagliptin to metformin.</p> <p>In the full analysis set, the HbA_{1c} change from baseline at week 24 was -0.38% (95% CI, -0.43 to -0.32) in the sitagliptin group and -0.55% (95% CI, -0.61 to -0.50) in the metformin group (difference, 0.18%; 95% CI, 0.10 to 0.25), which demonstrated the non-inferiority of sitagliptin to metformin.</p> <p>Secondary:</p> <p>The proportion of patients with an HbA_{1c} <7.0% at week 24 was greater with metformin (76%) compared with sitagliptin (69%; difference, -7.1%; 95% CI, -12.9 to -1.2).</p> <p>The proportion of patients with an HbA_{1c} <6.5% was not statistically different between the metformin (39%) and sitagliptin (34%) groups (difference, -5.6%; 95% CI, -11.8 to 0.8).</p> <p>The change from baseline in FPG was greater with metformin (-19.4 mg/dL) compared with sitagliptin (-11.5 mg/dL).</p> <p>The reduction in fasting proinsulin was greater in the metformin group, which resulted in a larger reduction in the proinsulin/insulin ratio at week 24.</p> <p>Both treatments produced similar increases in β-cell function and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>reductions in insulin resistance over 24 weeks.</p> <p>HDL-C was improved with both treatments. TGs were slightly reduced with sitagliptin. Small increases in TC were observed for each group, with a slightly greater increase for sitagliptin. Modest increases in LDL-C and non-HDL-C were observed with sitagliptin, but not metformin over 24 weeks.</p> <p>The incidence of drug-related adverse events was lower in the sitagliptin group than in the metformin group. The incidence of gastrointestinal adverse events overall was lower in the sitagliptin group compared with the metformin group (11.6 vs 20.7%, respectively). Hypoglycemia occurred at a low rate in both groups (1.7% with sitagliptin and 3.3% with metformin; P=0.116). Body weight was reduced from baseline in both the sitagliptin (-0.6 kg) and metformin (-1.9 kg; P<0.001).</p>
<p>Nichols et al.³⁵ (2007)</p> <p>Metformin vs sulfonylurea vs insulin vs TZDs</p>	<p>MC, OS, RETRO</p> <p>Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies</p>	<p>N=9,546</p> <p>≥12 months</p>	<p>Primary: Weight changes</p> <p>Secondary: Not reported</p>	<p>Primary: Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant.</p> <p>Secondary: Not reported</p>
<p>Russell-Jones et al.³⁶ (2012)</p> <p>DRUATION-4</p> <p>Exenatide ER 2</p>	<p>DB, DD, MC, PG, RCT</p> <p>Drug-naïve (patients excluded if treated with any</p>	<p>N=820</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of</p>	<p>Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>mg SC once weekly</p> <p>vs</p> <p>metformin 2,000 mg/day</p> <p>vs</p> <p>pioglitazone 45 mg/day</p> <p>vs</p> <p>sitagliptin 100 mg/day</p>	<p>antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m², and stable weight</p>		<p>patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported QOL</p>	<p>and sitagliptin, respectively.</p> <p>Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001).</p> <p>Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26).</p> <p>Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments.</p> <p>Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892).</p> <p>No clinically significant changes in serum lipids were observed with any treatment.</p> <p>Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329).</p> <p>Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment.</p> <p>All treatments resulted in improvements in perceived treatment satisfaction, weight-related quality of life, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported).</p>
<p>Simpson et al.³⁷ (2006)</p> <p>First-generation sulfonylurea</p> <p>vs</p> <p>glyburide</p> <p>vs</p> <p>metformin</p>	<p>RETRO</p> <p>New users of one oral diabetic agent</p>	<p>N=5,95</p> <p>~4.6 years</p>	<p>Primary: Mortality</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>An increased risk of death was associated with higher daily doses of first-generation sulfonylureas (adjusted HR, 2.1; 95% CI, 1.0 to 4.7) and glyburide (HR, 1.3; 95% CI, 1.2 to 1.4) compared to metformin (HR, 0.8; 95% CI, 0.7 to 1.1).</p> <p>Secondary:</p> <p>Not reported</p>
<p>Bolen et al.³⁸ (2007)</p> <p>Biguanides</p>	<p>MA (Analysis of 216 controlled trials and cohort studies, and 2 SR)</p>	<p>N=136 (articles on intermediate outcomes)</p>	<p>Primary: Intermediate outcomes: HbA_{1c}, body weight, BP,</p>	<p>Primary:</p> <p>Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA_{1c} level of about 1%).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs meglitinides vs TZDs vs α-glucosidase inhibitors vs second-generation sulfonylureas</p>	<p>Patients with type 2 diabetes</p>	<p>N=167 (articles on adverse events) N=68 (articles on microvascular outcomes and mortality) Duration varied</p>	<p>lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events</p>	<p>Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.</p> <p>TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C.</p> <p>TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP.</p> <p>Most agents except metformin increased body weight by 1 to 5 kg.</p> <p>In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05).</p> <p>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).</p> <p>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.</p> <p>Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).</p> <p>In cohort studies, TZDs were associated with higher risk for congestive</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.</p> <p>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.</p> <p>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.</p>
<p>Saenz et al.³⁹ (2005)</p> <p>Metformin monotherapy</p> <p>vs</p> <p>placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin</p>	<p>MA (29 RCTs)</p> <p>Adult patients with type 2 diabetes</p>	<p>N=5,259</p> <p>≥ 3 months</p>	<p>Primary:</p> <p>Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypoglycemia or</p>	<p>Primary:</p> <p>Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03).</p> <p>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02).</p> <p>Secondary:</p> <p>Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>hyperglycemia, and sudden death); all-cause mortality</p> <p>Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow</p>	
<p>Monami et al.⁴⁰ (2008)</p> <p>Metformin</p> <p>vs</p> <p>sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists</p>	<p>MA</p> <p>Patients with type 2 diabetes mellitus</p>	<p>N=7,890 (27 RCT)</p> <p>Variable duration</p>	<p>Primary: Reduction in HbA_{1c} at 16 to 36 months</p> <p>Secondary: Not reported</p>	<p>Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.</p> <p>In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.</p> <p>Secondary: Not reported</p>
<p>Amori et al.⁴¹ (2007)</p> <p>Incretin-based therapies (exenatide, liraglutide, sitagliptin, and vildagliptin†)</p>	<p>MA (29 RCTs)</p> <p>Type 2 diabetics</p>	<p>N=12,996</p> <p>Duration varied (12 to 52 weeks)</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, proportion of patients achieving an HbA_{1c}<7.0%</p>	<p>Primary: Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA_{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81).</p> <p>Specifically, no difference in the HbA_{1c} was found in OL, non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA_{1c} efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs non-incretin-based therapy (placebo or hypoglycemic agent)				Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21). Exenatide-treated patients were more likely to achieve an HbA _{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in non-inferiority trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.
Frederich et al. ⁴² (2010) Saxagliptin 2.5 to 10 mg QD vs glyburide, metformin, or placebo	SR Inadequately controlled type 2 diabetics	N=4,607 16 to 116 weeks	Primary: Composite of cardiovascular events, cardiovascular death, MI, and stroke Secondary: Not reported	Primary: There were 38 (1.1%) cardiovascular events with saxagliptin compared to 23 (1.8%) with the comparator drugs (RR, 0.59; 95% CI, 0.35 to 1.00). There were 23 (0.7%) cardiovascular deaths, MIs, and stroke events with saxagliptin compared to 18 (1.4%) with the comparator drugs (RR, 0.44; 95% CI, 0.24 to 0.82). There were seven (0.2%) cardiovascular deaths with saxagliptin compared to 10 (0.8%) with comparator drugs (RR, 0.24; 95% CI, 0.09 to 0.63). Secondary: Not reported
Singh et al. ⁴³ (2011) TZDs (pioglitazone, rosiglitazone) vs placebo, sulfonylurea, or metformin	MA, SR (13 RCTs) Type 2 diabetics	N=17,627 1 to 5.5 years (follow-up)	Primary: Any pneumonia or lower respiratory tract infection reported as an adverse event, pneumonia or lower respiratory tract infection reported as a serious adverse event Secondary: Not reported	Primary: TZDs are associated with a significantly increased risk for any pneumonia or lower respiratory tract infection compared to control (130/8,163 vs 100/9,464; RR, 1.40; 95% CI, 1.08 to 1.82; P=0.01). In addition TZDs were associated with a significantly increased risk of serious pneumonia or lower respiratory tract infection compared to control (111/7,391 vs 87/8,692; RR, 1.39; 95% CI, 1.05 to 1.83; P=0.02). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Louisa et al.⁴⁴ (2011)</p> <p>TZDs (pioglitazone, rosiglitazone)</p> <p>vs</p> <p>placebo or other hypoglycemic agents</p>	<p>MA (37 RCTs)</p> <p>Type 2 diabetics</p>	<p>N=3,000</p> <p>>3 months</p>	<p>Primary: Glycemic outcomes</p> <p>Secondary: Change in baseline BMI, lipid profile, BP, high-sensitivity CRP, and insulin sensitizing effect; cardiovascular and clinical endpoints</p>	<p>Primary: Both pioglitazone (WMD, -0.12%; 95% CI, -0.38 to -0.16) and rosiglitazone (WMD, -0.47%; 95% CI, -0.62 to -0.33) significantly decreased HbA_{1c}. Pioglitazone only demonstrated a significant decrease compared to placebo, while rosiglitazone significantly decreased HbA_{1c} compared to placebo and a sulfonylurea.</p> <p>Both pioglitazone (WMD, -9.16 mg/dL; 95% CI, -15.60 to -2.72) and rosiglitazone (WMD, -16.10 mg/dL; 95% CI, -22.20 to -10.01) significantly decreased FPG compared to control. Pioglitazone demonstrated a significant decrease compared to placebo, metformin, and voglibose†, while rosiglitazone significantly decreased FPG compared to placebo, metformin, and a sulfonylurea.</p> <p>Secondary: Pioglitazone and rosiglitazone had similar effects on BMI (pioglitazone: WMD, 0.57; 95% CI, 0.34 to 0.80 and rosiglitazone: WMD, 0.72; 95% CI, 0.29 to 1.14).</p> <p>Pioglitazone demonstrated a neutral effect of LDL-C (WMD, 3.89 mg/dL; 95% CI, -0.04 to 7.83) and TC (WMD, 2.30 mg/dL; 95% CI, -3.81 to 8.41).</p> <p>Rosiglitazone significantly increased LDL-C (WMD, 11.30 mg/dL; 95% CI, 7.80 to 14.79) and TC (WMD, 7.34 mg/dL; 95% CI, 2.34 to 12.31). Both agents had favorable effects on HDL-C and TGs.</p> <p>Pioglitazone produced a small decrease in DBP and SBP, while rosiglitazone demonstrated a neutral effect.</p> <p>In 13 trials, pioglitazone demonstrated a neutral effect on high sensitivity CRP, while rosiglitazone demonstrated a small improvement in high sensitivity CRP.</p> <p>Consistent increase in adiponectin and improvement in HOMA-IR were observed with both pioglitazone and rosiglitazone.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Richter et al.⁴⁵ (2006)</p> <p>Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials)</p> <p>or</p> <p>pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone)</p> <p>Some studies had more than 1 treatment arm.</p>	<p>MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG</p> <p>Adults with type 2 diabetes, trial duration of at least 24 weeks</p>	<p>22 trials</p> <p>N=6,200 randomized to pioglitazone treatment (total N not reported)</p> <p>24 weeks to 34.5 months</p>	<p>Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects</p> <p>Secondary: Health-related quality of life, HbA_{1c}</p>	<p>Four trials evaluated cardiovascular events as secondary endpoints. There were significant decreases in major cardiac events with both pioglitazone vs control (RR, 0.24; 95% CI, 0.09 to 0.63) and rosiglitazone vs control (RR, 0.41; 95% CI, 0.19 to 0.87).</p> <p>Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095).</p> <p>Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).</p> <p>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and -0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 kg/m². Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of HbA _{1c} compared to pioglitazone treatment (P values not reported).
Lincoff et al. ⁴⁶ (2007) Pioglitazone monotherapy vs metformin (1 trial), placebo (4 trials), sulfonylureas (6 trials) or rosiglitazone (1 trial) or pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo	DB, MA, RCT with placebo or active comparator Adult patients with type 2 diabetes and inadequate glycemic control	N=16,390 (19 trials) 4 months to 3.5 years	Primary: Composite of death from any cause, MI or stroke Secondary: Incidence of serious heart failure	Primary: Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09). Progressive separation of time-to-event curves became apparent after approximately one year of therapy. Secondary: Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).
Lago et al. ⁴⁷ (2007) Pioglitazone 15 to 45 mg/day (2 trials) or rosiglitazone 4 to 8 mg/day (5 trials) vs	MA of DB, RCTs of TZDs that reported risk estimates or frequency data for congestive heart failure and cardiovascular death Patients with	7 trials N=20,191 29.7 months (range, 12 to 48 months)	Primary: Development of congestive heart failure, risk of cardiovascular death Secondary: Not reported	Primary: Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). The overall event rate for congestive heart failure was 2.3% for patients receiving TZDs and 1.4% in the comparator group. Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of congestive heart failure across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo (4 trials), glibenclamide* (1 trial), glimepiride (1 trial), metformin (1 trial), or metformin plus nonspecified sulfonylurea (1 trial)</p> <p>Doses of comparators were not specified and 1 trial had 2 control groups.</p>	<p>prediabetes or type 2 diabetes (with and without cardiovascular disease), mean age 59.2 years, mean BMI 31 kg/m², mean baseline HbA_{1c} 7.72%</p>			<p>CI, 1.21 to 2.42; P=0.002). The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07).</p> <p>The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI, 0.63 to 1.32; P=0.63) or both TZDs (combined RR, 0.93; 95% CI, 0.67 to 1.29; P=0.68). The risk of cardiovascular death did not differ between both drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96).</p> <p>Secondary: Not reported</p>
<p>Mannucci et al.⁴⁸ (2008)</p> <p>Pioglitazone vs active comparators, placebo, no treatment</p>	<p>MA (94 trials)</p> <p>Patients treated with pioglitazone (with or without type 2 diabetes)</p>	<p>N=21,180</p> <p>Variable duration</p>	<p>Primary: All-cause mortality, non-fatal coronary event (defined as MI, unstable angina or coronary re-vascularization), non-fatal chronic heart failure requiring hospitalization</p> <p>Secondary: Not reported</p>	<p>Primary: In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality (P value not reported).</p> <p>In non-diabetic patients, only one death was observed occurring among pioglitazone-treated patients.</p> <p>In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR, 0.41; 95% CI, 0.23 to 0.72).</p> <p>When analyzing all trials, no significant reduction of mortality was observed with pioglitazone.</p> <p>Comparing different agents, pioglitazone was associated with a lower mortality rate compared to sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars, or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR, 0.22; 95% CI, 0.05 to 1.03), metformin (RR, 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR, 0.49; 95% CI, 0.04 to 5.36), glitazars (RR, 0.42; 95% CI, 0.11 to</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>1.61), or placebo (RR, 0.16; 95% CI, 0.02 to 1.45).</p> <p>In PROactive, pioglitazone significantly reduced the incidence of non-fatal coronary events (P value not reported).</p> <p>In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported.</p> <p>In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR, 0.82; 95% CI, 0.55 to 1.23).</p> <p>Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant.</p> <p>In PROactive, pioglitazone was associated with an increased risk for chronic heart failure. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR ,1.32; 95% CI, 0.88 to 1.98).</p> <p>Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not significant (P value not reported). When adding PROactive or excluding trials vs dual PPARα/γ agonists pioglitazone was associated with a significant increase of risk for chronic heart failure.</p> <p>In comparison with different agents, pioglitazone was associated with an increased risk of chronic heart failure in PC trials, while differences with sulfonylureas or glitazars did not reach significance.</p> <p>Secondary: Not reported</p>
Nagajothi et al. ⁴⁹ (2008) Pioglitazone	MA (5 trials) Patients treated with pioglitazone	N=not reported Duration varied	Primary: MI Secondary: Stroke,	Primary: The RR for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17). Secondary: The RR for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs active comparators (metformin and/or sulfonylurea) or placebo			revascularization, total mortality, cardiovascular mortality	The RR for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56). The RR for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11). The RR for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47).
Karter et al. ⁵⁰ (2005) Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies	Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001	N=23,440 10.2 months (mean)	Primary: Time-to-incident admission to hospital for congestive heart failure Secondary: Not reported	Primary: Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99). Secondary: Not reported
Singh et al. ⁵¹ (2007) Rosiglitazone vs control (placebo or other non-TZD oral hypoglycemic drug including glyburide or metformin)	MA of RCTs (available up to May 2007 and included ADOPT, DREAM and RECORD trials) of rosiglitazone of at least 12 months duration Study participants with impaired glucose tolerance or type 2 diabetes,	4 trials N=14,291 (n=6,421 rosiglitazone; n=7,870 control) 1 to 4 years	Primary: RR of MI, heart failure, and cardiovascular mortality Secondary: Not reported	Primary: Rosiglitazone significantly increased the risk of MI (94 vs 83; RR, 1.42; 95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control. There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53). Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; 95% CI, 0.80 to 1.23; P=0.92). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	studies monitored cardiovascular adverse events and provided numerical data on all adverse events			
<p>Nissen et al.⁵² (2007)</p> <p>Rosiglitazone monotherapy or combination therapy</p> <p>vs</p> <p>placebo or active comparators (including gliclazide†, glimepiride, glipizide, glyburide, insulin, and metformin)</p>	<p>MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and DREAM trials)</p> <p>Mean age of participants was 56 years, mean baseline HbA_{1c} 8.2%</p>	<p>42 trials</p> <p>n=15,560 for rosiglitazone; n=12,283 for comparator</p> <p>24 to 208 weeks</p>	<p>Primary: MI and death from cardiovascular causes</p> <p>Secondary: Not reported</p>	<p>Primary: Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03).</p> <p>Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06).</p> <p>Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24).</p> <p>Secondary: Not reported</p>
<p>Richter et al.⁵³ (2007)</p> <p>Rosiglitazone monotherapy (10 trials) vs glyburide (2 trials), metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial)</p>	<p>MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG</p> <p>Adults with type 2 diabetes, trial duration of at least 24 weeks</p>	<p>18 trials</p> <p>N=3,888 randomized to rosiglitazone treatment (total N not reported)</p> <p>24 weeks to 4 years (median 26 weeks)</p>	<p>Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects</p> <p>Secondary: Health-related QOL, metabolic control (HbA_{1c})</p>	<p>Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference).</p> <p>The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>or</p> <p>rosiglitazone combination therapy vs a similar combination with another compound (8 trials)</p> <p>Some studies had more than 1 treatment arm.</p>				<p>rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference).</p> <p>The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in BMI up to 1.5 kg/m². Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01).</p> <p>Secondary: No study investigated health-related quality of life.</p> <p>Active glucose-lowering compounds like metformin, glibenclamide* or glimepiride resulted in similar reductions of HbA_{1c} compared to rosiglitazone treatment.</p>
<p>Kheirbek et al.⁵⁴ (2013)</p> <p>Hypoglycemic medications</p>	<p>OS, RETRO</p> <p>Veterans with diabetes cared for at a Veterans</p>	<p>N=17,773</p> <p>Variable duration</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Not reported</p>	<p>Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use	Administration Capital area medical center			(OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions. Secondary: Not reported
Type 2 Diabetes – Combination Therapy				
Halimi et al. ⁵⁵ (2000) Metformin 850 mg BID to TID and acarbose 50 to 100 mg TID vs metformin 850 mg BID to TID	DB, PC, PG, RCT Patients 30 to 70 years of age with type 2 diabetes, BMI 25 to 35 kg/m ² , having poor glycemic control despite receiving metformin ≥2 months before the study start	N=152 6 months	Primary: HbA _{1c} at trial end Secondary: Blood glucose, insulin profiles, TG	Primary: Mean difference in HbA _{1c} from baseline to trial end was -0.7±1.2% with acarbose compared to 0.2±1.3% with placebo (P=0.0001). Patients were classified as responders if their HbA _{1c} values at trial end were <7.0% or had decreased by <15% relative to baseline. The total numbers of responders were 25 of 49 (42%) patients receiving acarbose and 12 of 70 (17%) patients receiving placebo (P=0.002). Secondary: Mean difference in the fasting blood glucose level from baseline to trial end was -1.0±2.8 mmol/L with acarbose compared to 1.3±2.8 mmol/L with placebo (P=0.0001). Mean difference in two-hour PPG level from baseline to trial end was -1.4±3.8 mmol/L with acarbose compared to 1.1±3.5 mmol/L with placebo (P=0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Phillips et al.⁵⁶ (2003)</p> <p>Metformin (usual dose) and acarbose 50 mg to 100 mg BID</p> <p>vs</p> <p>metformin (usual dose)</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥ 40 years of age with type 2 diabetes for ≥ 6 months, BMI 25 to 35 kg/m², HbA_{1c} 7.0 to 10.0% at screening week and 6.8 to 10.2% at baseline, and inadequately controlled by metformin</p>	<p>N=83</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG</p>	<p>Mean changes between acarbose compared to placebo for TG, fasting and postprandial serum insulin were not significant (P value not significant).</p> <p>Primary: Mean HbA_{1c} increased with placebo from 7.82\pm0.83% at baseline to 8.10\pm1.06% at week 12 and 8.50\pm1.44% at trial end. The mean increase after 24 weeks was 0.68\pm1.17%, with a significant overall time effect (P=0.0001).</p> <p>With acarbose, mean HbA_{1c} decreased from 8.02\pm0.85% at baseline to 7.78\pm1.00% at week 12 (P=0.0261). At the trial end, mean HbA_{1c} increased to 7.97\pm1.10%. There was no significant overall time effect for acarbose (P value not reported).</p> <p>Adjusted least square means for the change in HbA_{1c} from baseline to trial end showed a decrease of 0.16\pm0.18% with acarbose compared to an increase of 0.86\pm0.16% with placebo. There was a significant difference between the treatment groups of 1.02% (95% CI, 0.543 to 1.497; P=0.0001).</p> <p>Secondary: Mean FPG levels increased with placebo from baseline (9.41 \pm 1.99 mmol/L) to week 4 (10.06 \pm2.43 mmol/L) to trial end (10.77 \pm3.39 mmol/L). The levels only changed slightly with acarbose.</p> <p>Mean FPG increases were 1.36\pm2.88 mmol/L with placebo and 0.08\pm1.98 mmol/L with acarbose. The adjusted least square means showed increase at trial end with both treatments of 0.34\pm0.42 mmol/L with acarbose vs 1.48\pm0.39 mmol/L with placebo, with a significance of 1.132 mmol/L between the two treatments (95% CI, 0.056 to 2.208; P=0.0395).</p>
<p>Rosenstock et al.⁵⁷ (2016)</p> <p>Canagliflozin 100 mg and metformin XR (CANA100MET)</p>	<p>DB, RCT</p> <p>Patients with drug-naïve type 2 diabetes from 18 to 75 years of age</p>	<p>N=1,186</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Noninferiority in HbA_{1c} lowering with canagliflozin</p>	<p>Primary: At week 26, reductions from baseline in HbA_{1c} were seen with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET (-1.77, -1.78, -1.37, -1.42, and -1.30%, respectively), resulting in final mean HbA_{1c} values of 7.0, 7.0, 7.4, 7.3, and 7.4%, respectively. Reductions in HbA_{1c} with CANA100/MET and CANA300/MET were statistically significant versus MET (LS mean differences of -0.46% and -0.48%, respectively; P=0.001 for both) and versus CANA100 and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>Canagliflozin 300 mg and metformin XR (CANA300MET)</p> <p>vs</p> <p>Canagliflozin 100 mg (CANA 100)</p> <p>vs</p> <p>Canagliflozin 300 mg (CANA 300)</p> <p>vs</p> <p>metformin XR (MET)</p> <p>(Metformin XR doses were titrated)</p>			<p>monotherapy versus metformin; changes in FPG, body weight, and SBP; and proportion of patients achieving HbA_{1c} <7.0%</p>	<p>CANA300 (LS mean differences of -0.40% and -0.36%, respectively; P=0.001 for both).</p> <p>Secondary: Noninferiority of HbA_{1c} lowering was also demonstrated with CANA100 and CANA300 versus MET (LS mean differences of -0.06% and -0.11%, respectively; noninferiority P=0.001 for both). At week 26, significant differences in the proportion of patients who achieved HbA_{1c} <7.0% were observed with CANA100/MET and CANA300/MET versus MET (P=0.027 and P=0.016, respectively); 49.6%, 56.8%, 38.8%, 42.8%, and 43.0% of patients achieved HbA_{1c} <7.0% with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively.</p> <p>Dose-related reductions in FPG were observed with CANA100/MET and CANA300/MET that were greater compared with their respective monotherapies. At week 26, reductions in body weight from baseline were observed across groups (-3.2, -3.9, -2.8, -3.7, and -1.9 kg [-3.5%, -4.2%, -3.0%, -3.9%, and -2.1%] with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively). CANA100/MET, CANA300/MET, CANA100, and CANA300 provided modest reductions in SBP compared with MET (-2.2, -1.7, -2.2, -2.4, and -0.3 mmHg, respectively). Reductions in SBP with CANA100/MET and CANA300/MET were not statistically significant versus MET (LS mean differences of -1.9 and -1.3 mmHg, respectively).</p>
<p>Lopez-Alvarenga et al.⁵⁸ (1999)</p> <p>Metformin 1,200 mg daily, chlorpropamide 500 mg daily, and acarbose 100 mg TID</p> <p>vs</p>	<p>DB, RCT, XO</p> <p>Patients with type 2 diabetes from 35 to 70 years of age with BMI 23 to 35 kg/m², with a FPG >8.8 mmol/L despite maximal doses of chlorpropamide and metformin for at least 2 months</p>	<p>N=46</p> <p>42 weeks</p>	<p>Primary: Change in FPG from baseline, body weight, HbA_{1c}, fasting insulin, fasting C-peptide, intravenous glucose tolerance test (incremental area), glucose meal tests (incremental area)</p>	<p>Primary: Changes in FPG from baseline were not significant for placebo (P=0.62), but were significant for acarbose (P=0.05) and insulin (P=0.003).</p> <p>Changes in HbA_{1c} from baseline were not significant for placebo (P=0.62) and acarbose (P=0.3), but were significant for insulin (P=0.008).</p> <p>Changes in body weight were not significant in any group (P=0.2 vs baseline).</p> <p>Changes in fasting insulin from baseline were not significant for placebo (P=0.38), but were significant for acarbose (P=0.03) and insulin (P=0.02).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>metformin 1,200 mg daily, chlorpropamide 500 mg daily, and NPH insulin at bedtime</p> <p>vs</p> <p>metformin 1,200 mg daily, chlorpropamide 500 mg daily, and placebo</p>			<p>Secondary: Not reported</p>	<p>Changes in fasting C-peptide from baseline were not significant in any group, placebo (P=0.7), acarbose (P=0.5), and insulin (P=0.24).</p> <p>Changes in intravenous glucose tolerance test (incremental area) from baseline were not significant in any group, placebo (P=0.36), acarbose (P=0.91), and insulin (P=0.94).</p> <p>Changes in glucose meal tests (incremental area) from baseline were not significant for placebo (P=0.84) and insulin (P=0.08), but were for acarbose (P=0.02).</p> <p>Changes in insulin (incremental area) from baseline were not significant for any group, placebo (P=0.92), acarbose (P=0.3), and insulin (P=0.43).</p> <p>Thirty-seven percent of patients developed severe bloating during acarbose use. This was significant (P<0.05) compared to acarbose and placebo or insulin.</p> <p>Secondary: Not reported</p>
<p>Haak et al.⁵⁹ (2012)</p> <p>Linagliptin 5 mg QD</p> <p>vs</p> <p>metformin 500 mg BID</p> <p>vs</p> <p>metformin 1,000 mg BID</p> <p>vs</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve (HbA_{1c} 7.5 to 11.0%) or who had received one other oral antidiabetic drug (HbA_{1c} 7.0 to 10.5%)</p>	<p>N=791</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1c} at week 24</p> <p>Secondary: Change from baseline in FPG, change from baseline in HbA_{1c} and FPG over time, proportion of patients requiring rescue therapy after failing to achieve pre-specified glycemic</p>	<p>Primary: After 24 weeks, the mean change in HbA_{1c} was 0.1% with placebo, -0.5% with linagliptin 5 mg QD, -0.6% with metformin 500 mg BID, -1.1% with metformin 1,000 mg BID, -1.2% with linagliptin plus metformin 500 mg, and -1.6% with linagliptin plus metformin 1,000 mg.</p> <p>The adjusted placebo-corrected mean changes in HbA_{1c} were -1.7% (95% CI, -2.0 to -1.4) for linagliptin plus metformin 1,000 mg; -1.3% (95% CI, -1.6 to -1.1) for linagliptin plus metformin 500 mg; -1.2% (95% CI, -1.5 to -0.9) for metformin 1,000 mg; -0.8% (95% CI, -1.0 to -0.5) for metformin 500 mg, and -0.6% (95% CI, -0.9 to -0.3) for linagliptin monotherapy (P<0.0001 for all).</p> <p>The mean treatment differences for linagliptin plus metformin 1,000 mg vs metformin and linagliptin monotherapy were -0.5% (95% CI, -0.7 to -0.3) and -1.1% (95% CI, -1.4 to -0.9), respectively. For linagliptin plus metformin 500 mg, the respective mean differences were -0.6% (95% CI, -</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>linagliptin 2.5 mg BID and metformin 500 mg BID</p> <p>vs</p> <p>linagliptin 2.5 mg BID and metformin 1,000 mg BID</p> <p>vs</p> <p>placebo</p>			<p>targets or discontinuing because of lack of efficacy, safety</p>	<p>0.8 to -0.4) and -0.8% (95% CI, -1.0 to -0.6; $P < 0.0001$ for all).</p> <p>Secondary: The adjusted placebo-corrected mean changes in FPG from baseline were -3.3 mmol/L (95% CI, -4.0 to -2.6) and -2.4 mmol/L (95% CI, -3.1 to -1.7) in the linagliptin plus metformin 1,000 mg and linagliptin plus metformin 500 mg groups, respectively. This is compared to -2.3 mmol/L (95% CI, -3.0 to -1.7), -1.4 mmol/L (95% CI, -2.1 to -0.8) and -1.0 mmol/L (95% CI, -1.7 to -0.3) in the metformin 1,000 mg, metformin 500 mg, and linagliptin monotherapy groups, respectively ($P < 0.0001$ for all).</p> <p>The proportion of patients requiring rescue therapy for inadequate glycemic control at week 24 was lower in the combination therapy groups (linagliptin plus metformin 1,000 mg, 4.3%; linagliptin plus metformin 500 mg, 7.3%) compared to either monotherapy alone (metformin 1,000 mg, 8.0%; metformin 500 mg, 13.5%; linagliptin, 11.1%).</p> <p>The proportion of patients reporting adverse events were comparable across the active treatment groups.</p>
<p>Haak et al.⁶⁰ (2013)</p> <p>linagliptin 2.5 mg plus metformin 500 mg (both twice daily)</p> <p>vs</p> <p>linagliptin 2.5 mg plus metformin 1000 mg (both twice daily)</p> <p>vs</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve (HbA_{1c} 7.5 to 11.0%) or who had received one other oral antidiabetic drug (HbA_{1c} 7.0 to 10.5%)</p> <p>(extension study of Haak et al.⁵²)</p>	<p>N=566</p> <p>54 weeks</p>	<p>Primary: Safety</p> <p>Secondary: Change from baseline in HbA_{1c} and FPG, the percentages of patients who achieved target HbA_{1c} levels of < 7.0 or < 6.5%, the percentages of patients with a reduction in HbA_{1c} levels of ≥ 0.5%, and use of rescue therapy</p>	<p>Primary: The incidences of treatment-emergent AEs during the extension period were comparable across the groups, ranging between 66 and 77%. Most adverse events were of mild or moderate intensity, with the majority considered unrelated to study drug.</p> <p>Secondary: All three groups maintained the reduction in HbA_{1c} achieved at the end of the six-month trial, with changes of $0.12 \pm 0.72\%$, $0.08 \pm 0.74\%$ and $0.13 \pm 0.54\%$, for the metformin 1000 group, linagliptin 2.5 + metformin 500, and linagliptin 2.5 + metformin 1000 groups, respectively.</p> <p>The overall incidence of rescue medication use was lower in the linagliptin 2.5 + metformin 1000 treatment group (14.0%) than in the linagliptin 2.5 + metformin 500 (27.6%) and metformin 1000 (24.7%) treatment groups. During the extension study, there were no clinically meaningful changes in weight, with mean \pmSD changes of -0.4 ± 2.7 kg, 0.2 ± 3.0 kg and -0.7 ± 3.2 kg in the metformin 1000, linagliptin 2.5 + metformin 500, and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 1000 mg twice daily monotherapy				linagliptin 2.5 + metformin 1000 groups, respectively.
Standl et al. ⁶¹ (2001) Metformin 500 to 850 mg daily, miglitol 25 mg to 100 mg TID, and glibenclamide* 3.5 to 5 mg BID to QID vs metformin 500 to 850 mg daily and glibenclamide* 3.5 to 5 mg BID to QID	DB, MC, PC, PG, RCT Patients 30 to 70 years of age with type 2 diabetes for ≥ 3 years; HbA _{1c} ≥ 7.5 to $\leq 10.5\%$; BMI ≤ 35 kg/m ² ; stable body weight over the previous 3 months; and inadequately controlled on combination therapy of diet, glibenclamide* and metformin	N=154 24 weeks	Primary: Change in baseline HbA _{1c} Secondary: FPG, PPG, fasting and postprandial serum insulin, TG, urinary glucose	Primary: Miglitol produced a significant reduction in HbA _{1c} (-0.55%; P=0.04) and PPG (-2.6 mmol/L; P=0.0009) compared to placebo. Secondary: FPG decreased with miglitol and was almost unchanged with placebo; the difference was not significant (P=0.10). Fasting insulin levels were unchanged with both treatments throughout the trial, with no significant difference between them (P=0.79). Postprandial insulin decreased from baseline to trial end, but the difference between the groups was not significant (P=0.26). Postprandial TG decreased slightly with miglitol and remained unchanged with placebo, and the difference was not significant (P=0.47).
Van Gaal et al. ⁶² (2001) Metformin 500 mg TID or 850 mg BID to TID and miglitol 25 to 100 mg TID vs metformin 500 mg TID or 850 mg BID to TID	DB, MC, PC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes for ≥ 1 year, HbA _{1c} ≥ 7.5 to $\leq 10.5\%$, BMI 23 to 40 kg/m ² , stable body weight over the previous 3 months, and whose diabetes was inadequately controlled by diet and metformin	N=152 32 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in FPG, PPG, serum insulin, fasting and one-hour postprandial TG levels	Primary: There was a significant decrease in HbA _{1c} with miglitol compared to placebo (-0.21 vs 0.22%; P=0.011). Secondary: PPG decreased with both treatments, but the reduction was more significant with miglitol (from 16.5 \pm 3.8 mmol/L at baseline to 13.8 \pm 5.0 mmol/L at trial end) compared to placebo (from 16.3 \pm 3.4 mmol/L at baseline to 15.7 \pm 3.8 mmol/L at trial end). The baseline adjusted means were 13.8 mmol/L with miglitol vs 15.8 mmol/L with placebo (P=0.0007). Fasting insulin levels decreased more with miglitol compared to placebo, the difference was not significant (P value not reported). FPG, fasting and postprandial TG levels showed a descriptive advantage for miglitol, but did not reach a statistical difference. Mean FPG levels fell

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				more with miglitol (baseline, 11.5±2.7 mmol/L; end of treatment, 10.8±3.6 mmol/L) compared to placebo (baseline, 11.6±3.1 mmol/L; end of treatment, 11.5±3.4 mmol/L; difference of adjusted means; P=0.15). Fasting TG levels fell with miglitol (treatment effect, -16.3 mg/dL) compared to placebo (treatment effect, 3.77 mg/dL; P=0.26). Similar results were seen for postprandial TG.
Chiasson et al. ⁶³ (2001) Metformin 500 mg TID and miglitol 100 mg TID vs metformin 500 mg TID vs miglitol 100 mg TID vs placebo	DB, MC, PC, RCT Patients >40 years of age with type 2 diabetes inadequately controlled by diet alone, HbA _{1c} 7.2 to 9.5%	N=324 36 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG and PPG, insulin levels, and TG	Primary: Mean change in HbA _{1c} from baseline was 0.38±0.12% with placebo, 0.02±0.10% with miglitol, -0.85±0.12% with metformin, and -1.39±0.11% with combination therapy. A reduction in mean placebo-subtracted HbA _{1c} of -1.78% was seen with combination therapy, and this was significantly different from metformin (-1.25%; P=0.002). Mean reductions in HbA _{1c} compared to placebo were -0.37% with miglitol, -1.25% with metformin, and -1.78% with combination therapy. The end of treatment mean HbA _{1c} was 8.5% with placebo, 8.2% with miglitol, 7.3% with metformin, and 6.9% with combination therapy. Significantly more patients (P=0.0014) receiving combination therapy (70.6%) were classified as responders (i.e., showed ≥15% reduction from baseline in HbA _{1c} or achieved an HbA _{1c} <7.0%) compared to metformin (45.5%). Secondary: Combination therapy resulted in better metabolic control compared to metformin for FPG (P=0.0025) and two-hour PPG AUC (P=0.0001). Changes in TG levels from baseline to trial end did not differ significantly between combination therapy compared to metformin, and showed no consistent trend (P value not reported).
DeFronzo et al. ⁶⁴ (2009) Metformin (existing therapy) and saxagliptin 2.5, 5, or 10 mg QD	DB, PC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA _{1c} ≥7.0 to ≤10.0%), receiving	N=743 24 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG and PPG AUC _{0-3hr} ,	Primary: Saxagliptin significantly decreased HbA _{1c} compared to placebo (-0.59, -0.69, and -0.58 vs 0.13%; P<0.0001 for all), with significance achieved after four weeks. Secondary: Saxagliptin significantly decreased FPG compared to placebo (-14.31, -22.03, and -20.50 vs 1.24 mg/dL; P<0.0001 for all). Similar results were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metformin (existing therapy) and placebo	stable doses of metformin ($\geq 1,500$ to $< 2,550$ mg/day) ≥ 8 weeks, fasting C-peptide concentration ≥ 1 ng/mL, and BMI ≤ 40 kg/m ²		proportion of patients achieving an HbA _{1c} $< 7.0\%$	observed with PPG AUC _{0-3hr} (-8,891, -9,586, and -8,137 vs -3,291 [mg/minute]/[dL]; P < 0.0001 for all). A significantly greater proportion of patients achieved an HbA _{1c} $< 7.0\%$ with saxagliptin compared to placebo (37.1, 43.5, and 44.4 vs 16.6%; P < 0.0001 for all).
Hermans et al. ⁶⁵ (2012) PROMPT Fixed-dose metformin 1500 mg/day, plus either: Add-on saxagliptin 5 mg/day (SAXA-MET) vs metformin uptitration (MET-UP) to a max dose (2500 mg/day).	DB, RCT metformin-tolerant patients ≥ 18 years of age with type 2 diabetes and insufficient glycemic control on submaximal metformin therapy	N=286 24 weeks	Primary: Absolute change from baseline in HbA _{1c} Secondary: Proportion of patients achieving a therapeutic glycemic response, change from baseline in FPG, safety and tolerability	Primary: Compared with baseline, an adjusted mean change in HbA _{1c} at Week 24 of -0.47% was observed in the SAXA-MET group and -0.38% in the MET-UP group. The difference in adjusted mean change from baseline HbA _{1c} between treatment groups was -0.10%, which was not statistically significant (P=0.260). Secondary: The proportion of patients achieving therapeutic glycemic response (HbA _{1c} $< 7\%$) at Week 24 was 43.8% (SAXA-MET) and 35.0% (MET-UP). In comparison, the proportion of patients achieving therapeutic glycemic response (HbA _{1c} $\leq 6.5\%$) at Week 24 was 20.5% (SAXA-MET) and 16.8% (MET-UP). During the 24-week treatment period, 51.0% (75/147) of patients in the SAXA-MET group and 43.9% (61/139) in the MET-UP group experienced at least one adverse event.
Pfutzner et al. ⁶⁶ (2011) Saxagliptin 5 and 10 mg QD plus metformin 500 mg/day vs	AC, DB, ES, MC, RCT Type 2 diabetics 18 to 77 years of age, HbA _{1c} ≥ 8.0 to $\leq 12.0\%$, fasting C-peptide concentration ≥ 1 ng/mL, and BMI	N=1,306 52 weeks (76 weeks total)	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline body weight, proportion of patients achieving an HbA _{1c} < 7.0 and	Primary: Decreases in HbA _{1c} with saxagliptin 5 mg plus metformin were -2.31% (95% CI -2.44 to -2.18) and -2.33% (95% CI -2.46 to -2.20) with saxagliptin 10 mg plus metformin compared to -1.55 (95% CI, -1.70 to -1.40) and -1.79% (95% CI, -1.93 to -1.65) with saxagliptin and metformin monotherapies, respectively; P < 0.0001 for combination therapy vs monotherapy). Secondary: Decreases in body weight were -1.2 kg with saxagliptin 5 mg plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
saxagliptin 10 mg QD vs metformin 500 mg/day	≤40 kg/m ²		≤6.5%	metformin, -0.7 kg with saxagliptin 10 mg plus metformin, -0.3 kg with saxagliptin, and -1.0 kg with metformin (P values not reported). A greater proportion of patients achieved an HbA _{1c} <7.0% with saxagliptin 5 mg plus metformin and saxagliptin 10 mg plus metformin compared to saxagliptin and metformin (51.5 and 50.5 vs 25.0 and 34.7%, respectively; P values not reported). Similar results were observed with HbA _{1c} <6.5% (P values not reported).
Jadzinsky et al. ⁶⁷ (2009) Metformin 500 to 2,000 mg daily and saxagliptin 5 mg QD vs metformin 500 to 2,000 mg daily and saxagliptin 10 mg QD vs metformin 500 to 2,000 mg daily vs saxagliptin 10 mg QD	AC, DB, MC, RCT Type 2 diabetics 18 to 77 years of age, HbA _{1c} ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m ²	N=1,306 24 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG and PPG AUC _{0-3hr} , proportion of patients achieving an HbA _{1c} <7.0 and ≤6.5%, proportion of patients requiring rescue for failing to achieve prespecified glycemic targets or discontinuing for lack of efficacy at 24 weeks	Primary: Combination therapy significantly decreased HbA _{1c} compared to monotherapy with either saxagliptin or metformin (-2.5 and -2.5 vs -1.7 and -2.0%, respectively; P<0.0001 vs monotherapy for all). Secondary: Combination therapy significantly decreased FPG compared to monotherapy with either saxagliptin or metformin (P=0.0002 for saxagliptin 5 mg plus metformin vs saxagliptin and P<0.001 for saxagliptin 10 mg plus metformin vs saxagliptin and metformin). Similar results were observed for PPG AUC _{0-3hr} (P<0.0001 for all vs monotherapy). The proportion of patients achieving an HbA _{1c} <7.0% was significantly greater with combination therapy compared to monotherapy with either agent (60.3 and 59.7 vs 32.2 and 41.1%; P<0.0001 for all vs monotherapy). Similar results were observed for HbA _{1c} ≤6.5% (45.3 and 40.6 vs 20.3 and 29.0%; P<0.0001 for saxagliptin 5 mg plus metformin vs saxagliptin and metformin; P<0.0001 for saxagliptin 10 mg plus metformin vs saxagliptin, and P=0.0026 for saxagliptin 10 mg plus metformin vs metformin). At week 24, 7.5% of patients receiving saxagliptin 5 mg plus metformin and 21.2% of patients receiving saxagliptin 10 mg were discontinued or rescued for lack of glycemic control (P<0.0001). No significance was observed when saxagliptin 5 mg plus metformin was compared to metformin (P=0.2693). Similar results were observed with saxagliptin 10 mg plus metformin compared to either monotherapy (P<0.0001 vs saxagliptin 10 mg and P=0.0597 vs metformin).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Derosa et al.⁶⁸ (2010)</p> <p>Sitagliptin 100 mg QD</p> <p>vs</p> <p>metformin 850 mg BID</p> <p>All patients were receiving pioglitazone (15 or 30 mg/day).</p>	<p>DB, RCT</p> <p>Patients with type 2 diabetes, HbA_{1c} >7.5%, and receiving pioglitazone 30 mg/day</p>	<p>N=151</p> <p>12 months</p>	<p>Primary: Body weight, BMI, HbA_{1c}, FPG, PPG, fasting plasma insulin, HOMA-IR, HOMA-B, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, adiponectin, resistin, TNF-α, high sensitivity CRP</p> <p>Secondary: Not reported</p>	<p>Primary: A decrease in body weight and BMI were observed in patients receiving metformin, which was not observed in patients receiving sitagliptin.</p> <p>Significant decreases in HbA_{1c}, FPG, and PPG, and significant increases in HOMA-B were comparable between the two treatment groups.</p> <p>Fasting plasma insulin, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, and HOMA-IR were decreased with both treatments. While values were lower with metformin, there were no significant differences observed between the two treatments.</p> <p>Sitagliptin achieved no significant changes in changes in adiponectin, resistin, TNF-α, compared to a significant increase in adiponectin and significant decreases in resistin and TNF-α achieved with metformin.</p> <p>High sensitivity CRP decreased significantly with both treatments, with no difference between them.</p> <p>Secondary: Not reported</p>
<p>Goldstein et al.⁶⁹ (2007)</p> <p>Sitagliptin 50 mg BID plus metformin 500 and 1,000 mg BID</p> <p>vs</p> <p>sitagliptin 100 mg QD</p> <p>vs</p> <p>metformin 500 and</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetics 18 to 78 years of age and an HbA_{1c} of 7.5 to 11.0%</p>	<p>N=1,091</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, lipid profiles, β cell function, insulin resistance; adverse events</p>	<p>Primary: Decreases in HbA_{1c} were significant with all active treatments as compared to placebo and for combination therapy compared to monotherapy (P<0.001). There was an additive effect seen in the combination treatment groups. The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with all active treatments compared to placebo (P<0.001).</p> <p>Secondary: Significant decreases in FPG were achieved between combination therapy and monotherapy, and between all active treatments compared to placebo (P<0.001).</p> <p>Data on fasting serum insulin and lipid profiles were not reported.</p> <p>Combination therapy demonstrated an additive effect, as compared to</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1,000 mg BID vs placebo				<p>monotherapy, with regards to improvements in β cell function.</p> <p>HOMA-B increased with all active treatments compared to placebo ($P<0.001$). The combination therapy significantly increased HOMA-B compared to monotherapy (sitagliptin and low-dose metformin; $P\leq 0.001$).</p> <p>Significant improvements in the proinsulin:insulin ratio observed with all active treatments compared to placebo ($P<0.05$). Differences between combination therapy and monotherapy were also significant ($P<0.05$).</p> <p>The incidence of adverse events was similar between combination therapy and metformin. Gastrointestinal adverse events including diarrhea, nausea, abdominal pain, and vomiting were most frequently observed with metformin high-dose both as monotherapy and combination therapy. A low frequency of hypoglycemia was similar among all treatments (0.6 to 2.2%). No change in weight was observed with sitagliptin compared to all other active treatments, where there was a significant decrease in body weight (-0.6 to -1.3 kg; $P<0.05$) and placebo (-0.9 kg; $P<0.01$).</p>
<p>Reasner et al.⁷⁰ (2011)</p> <p>Sitagliptin/metformin 50/500 to 1,00 mg BID</p> <p>vs</p> <p>metformin 500 to 1,000 mg BID</p>	<p>DB, MC, PG, RCT</p> <p>Treatment-naïve type 2 diabetics 18 to 78 years of age, and an $HbA_{1c} \geq 7.5\%$</p>	<p>N=1,250</p> <p>18 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving an $HbA_{1c} < 7.0$ and $< 6.5\%$, change in baseline FPG, proinsulin:insulin ratio, and β cell function</p>	<p>Primary: Combination therapy significantly decreased HbA_{1c} compared to metformin (-2.4 vs -1.8%; $P<0.001$).</p> <p>Secondary: A significantly greater proportion of patients receiving combination therapy achieved an $HbA_{1c} < 7.0\%$ (49.2 vs 34.2%, respectively; $P<0.001$) and $< 6.5\%$ (31.8 vs 16.0%, respectively; $P<0.001$) compared to patients receiving metformin.</p> <p>Combination therapy significantly decreased FPG compared to metformin (-3.8 vs -3.0 mg/dL; $P<0.001$).</p> <p>Combination therapy significantly decreased proinsulin:insulin ratio compared to metformin (-0.238 vs -0.186; $P<0.05$).</p> <p>Combination therapy significantly improved β cell function compared to metformin ($P<0.05$).</p>
Raz et al. ⁷¹	DB, MC, PC, PG,	N=190	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2008)</p> <p>Metformin 1,500 to 2,550 mg daily and sitagliptin 100 mg daily</p> <p>vs</p> <p>metformin 1,500 to 2,550 mg daily and placebo</p>	<p>RCT</p> <p>Type 2 diabetics 18 to 78 years of age, HbA_{1c} 7.0 to 10.0% receiving metformin or other oral antihyperglycemic agents as monotherapy or being treated with metformin in combination with other oral antihyperglycemic agents</p>	<p>30 weeks</p>	<p>Change in baseline HbA_{1c} at 18 weeks</p> <p>Secondary: Change in baseline FPG at 18 weeks, two-hour PPG at 18 weeks, and HbA_{1c} at 30 weeks; safety and tolerability</p>	<p>Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -1.0%; 95% CI, -1.4 to -0.7; P<0.001). Numerically greater decreases in HbA_{1c} were observed in patients with a higher baseline HbA_{1c}. A greater proportion of patients receiving sitagliptin achieved an HbA_{1c}<7.0% at weeks 18 and 30 compared to patients receiving placebo (13.7 and 22.1 vs 3.3 and 3.3%; P values not reported).</p> <p>Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -1.4 mmol/L; 95% CI, -2.1 to -0.7; P<0.001).</p> <p>Sitagliptin significantly decreased two-hour PPG compared to placebo (treatment difference, -3.0 mmol/L; 95% CI, -4.2 to -1.9; P<0.001).</p> <p>Sitagliptin significantly decreased HbA_{1c} compared to placebo at week 30 (treatment difference, -1.0%; 95% CI, -1.4 to -0.6; P<0.001).</p> <p>The incidence of adverse events was similar with both treatments. No serious adverse events or discontinuations due to clinical adverse events were reported with sitagliptin. With placebo, there were six serious clinical adverse events that resulted in one death and two discontinuations. None of the adverse events were deemed to be drug-related. There were no differences between the two treatments in the incidences of hypoglycemia or gastrointestinal adverse events (abdominal pain, nausea, vomiting, and diarrhea). Over the 30 week period a small decrease in weight of 0.5 kg was observed with both treatments.</p>
<p>Derosa et al.⁷² (2012)</p> <p>metformin + placebo</p> <p>vs</p> <p>metformin + sitagliptin</p>	<p>DB, MC, PC, RCT</p> <p>Type 2 diabetic patients aged >18, drug-naïve, with poor glycemic control (HbA_{1c} level >8.0%), and overweight (body mass index [BMI] ≥25 and <30)</p>	<p>N=178</p> <p>12 months</p>	<p>Primary: BMI, glycemic control, fasting plasma insulin (FPI), homeostasis model assessment insulin resistance index (HOMA-IR), homeostasis model assessment β-cell function index</p>	<p>Primary: A similar decrease of body weight and BMI was observed with both treatments at 12 months (P<0.05 for both), without any difference between the two groups.</p> <p>HbA_{1c} and PPG improved in both groups at six (P<0.05), nine (P< 0.01), and 12 months (P<0.001) with sitagliptin + metformin, and at nine (P<0.05) and 12 months (P<0.01) with placebo + metformin, even though sitagliptin + metformin were more effective than placebo + metformin in reducing HbA_{1c}, and PPG at 12 months (P<0.05). FPG obtained with sitagliptin + metformin was significantly lower compared to the value</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients underwent a run-in period of 8±2 months of metformin monotherapy	kg/m ²)		(HOMA-β), fasting plasma proinsulin (FPPr), proinsulin/fasting plasma insulin ratio (Pr/FPI ratio), C-peptide, glucagon, adiponectin (ADN), and high sensitivity-C reactive protein (Hs-CRP). Secondary: Not reported	reached with placebo + metformin at 12 months (P<0.05). Most other parameters achieved favorable change from baseline but no significant difference between treatment groups. Sitagliptin + metformin resulted better than placebo + metformin in reducing HOMA-IR and glucagon at 12 months (P<0.05). Secondary: Not reported
Perez-Monteverde et al. ⁷³ (2011) Sitagliptin/metformin vs pioglitazone 30 to 45 mg QD In Phase 1, patients were randomized to either sitagliptin 100 mg QD or pioglitazone 30 mg QD. In Phase 2, patients randomized to	DB, RCT Patients with type 2 diabetes and HbA _{1c} 7.5 to 12.0%	N=492 (Phase 1) 12 weeks (Phase 1) plus 28 weeks (Phase 2)	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG and 2-hour PPG, proportion of patients achieving HbA _{1c} <7.0%, safety, body weight	Primary: At the end of Phase 1 (12 weeks), mean changes from baseline in HbA _{1c} were -1.0 and -0.9% with sitagliptin and pioglitazone. At the end of Phase 2 (40 weeks), improvements in HbA _{1c} were greater with combination therapy compared to pioglitazone (-1.7 vs -1.4%; P=0.002). Secondary: At the end of Phase 1 (12 weeks), mean changes from baseline were -26.6 and -28.0 mg/dL for FPG and -52.8 and -50.1 mg/dL for two-hour PPG. At the end of Phase 2 (40 weeks), improvements in FPG and two-hour PPG were greater with combination therapy compared to pioglitazone (-45.8 vs -37.6 mg/dL; P=0.03 and -90.3 vs -69.1 mg/dL; P=0.001). Significantly more patients receiving combination therapy achieved an HbA _{1c} <7.0% (55.0 vs 40.5%; P=0.004). A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of edema were observed with combination therapy compared to pioglitazone. The incidence of hypoglycemia was similarly low with both treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>sitagliptin in Phase 1 were switched to sitagliptin/metformin, and patients randomized to pioglitazone in Phase 1 were up titrated to 45 mg/day.</p>				<p>Body weight decreased with combination therapy and increased with pioglitazone (-1.1 vs 3.4 kg; P<0.001).</p>
<p>Wainstein et al.⁷⁴ (2012)</p> <p>Sitagliptin/metformin 50/500 mg BID, titrated up to 50/1,000 mg BID</p> <p>vs</p> <p>pioglitazone 30 mg/day, titrated up to 45 mg/day</p>	<p>DB, RCT</p> <p>Treatment-naïve patients with type 2 diabetes HbA_{1c} 7.5 to 12.0%</p>	<p>N=517</p> <p>32 weeks</p>	<p>Primary: Change from baseline HbA_{1c}, proportion of patients who achieved HbA_{1c} <7.0%</p> <p>Secondary: Change from baseline FPG</p>	<p>Primary: The least squares mean changes in HbA_{1c} at week 32 were -1.9 and -1.4% with combination therapy compared to pioglitazone, respectively (between-group differences, -0.5%; P<0.001).</p> <p>A greater proportion of patients achieved an HbA_{1c} <7.0% at week 32 with combination therapy compared to pioglitazone (57 vs 43%; P<0.001).</p> <p>Secondary: Compared to pioglitazone, combination therapy resulted in a greater least squares mean reductions in FPG (-56.0 vs -44.0 mg/dL; P<0.001) and 2-hour PPG (-102.2 vs -82.0 mg/dL; P<0.001) at week 32. A substantially greater reduction in FPG (-40.5 vs -13.0 mg/dL; P<0.001) was observed at week 1 with combination therapy compared to pioglitazone.</p> <p>A greater reduction in the fasting proinsulin:insulin and a greater increased in HOMA-B were observed with combination therapy compared to pioglitazone, while greater decreases in fasting insulin and HOMA-IR, and a greater increase in quantitative insulin sensitivity check index were observed with pioglitazone compared to combination therapy.</p> <p>Combination therapy resulted in a decrease in body weight (-1.4 kg) and pioglitazone resulted in an increase in body weight (3.0 kg; P<0.001).</p> <p>Higher incidences of diarrhea (15.3 vs 4.3%; P<0.001), nausea (4.6 vs 1.2%; P=0.02), and vomiting (1.9 vs 0.0%; P=0.026), and a lower incidence of edema (1.1 vs 7.0%; P<0.001) were observed with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>combination therapy compared to pioglitazone.</p> <p>There was no difference between the two treatments in the incidence of hypoglycemia (8.4 vs 8.3%; P=0.055).</p>
<p>Scott et al.⁷⁵ (2008)</p> <p>Metformin (existing therapy) and sitagliptin 100 mg QD</p> <p>vs</p> <p>metformin (existing therapy) and rosiglitazone 8 mg QD</p> <p>vs</p> <p>metformin and placebo</p>	<p>AC, DB, MC, PG, RCT</p> <p>Type 2 diabetics 18 to 75 years of age receiving stable metformin doses ($\geq 1,500$ mg/day for ≥ 10 weeks) and inadequate glycemic control ($HbA_{1c} \geq 7.0$ and $\leq 11.0\%$)</p>	<p>N=273</p> <p>18 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, β cell function, insulin resistance, and lipid profile</p>	<p>Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.50%; 95% CI, -0.87 to -0.60; $P \leq 0.001$). Similar results were observed with rosiglitazone (treatment difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). There was no difference between sitagliptin and rosiglitazone (treatment difference, -0.06%; 95% CI, -0.25 to 0.14).</p> <p>The proportion of patients achieving an $HbA_{1c} < 7.0\%$ was significantly greater with sitagliptin (55%; $P = 0.006$) and rosiglitazone (63%; P value not reported) compared to placebo (38%). There was no difference between sitagliptin and rosiglitazone (treatment difference, 8%; 95% CI, -6 to 22; P value not reported).</p> <p>Secondary: Sitagliptin (treatment difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; $P \leq 0.001$) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo.</p> <p>Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported).</p> <p>Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; $P \leq 0.05$) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported).</p> <p>Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported).</p> <p>Rosiglitazone significantly decreased fasting serum insulin compared to placebo (treatment difference, -3.4 μIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 μIU/mL; 95% CI, -5.50 to -1.40; P value not reported).</p> <p>The proinsulin:insulin ratio was similar across all treatments.</p> <p>Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; $P \leq 0.05$) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin (treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; $P \leq 0.05$) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported).</p>
<p>Hermansen et al.⁷⁶ (2007)</p> <p>Sitagliptin 100 mg QD, glimepiride 4 to 8 mg daily, and metformin 1,500 to 3,000 mg daily</p> <p>vs</p> <p>sitagliptin 100 mg QD plus</p>	<p>DB, DD, MC, PC, PG, RCT</p> <p>Type 2 diabetics 18 to 75 years of age, HbA_{1c} 6.7 to 10.6%, and inadequately controlled on glimepiride with or without metformin</p>	<p>N=441</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, plasma lipids, β cell function, and insulin resistance; safety and tolerability</p>	<p>Primary: Sitagliptin significantly decreased HbA_{1c} ($P < 0.001$) compared to placebo (treatment difference, -0.74%; 95% CI, -0.90 to -0.57). Patients who were receiving triple therapy (-0.89%; 95% CI, -1.10 to -0.68) had a significantly greater decrease in HbA_{1c} compared to patients receiving combination therapy (-0.57%; 95% CI, -0.82 to -0.32).</p> <p>A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (17.1 vs 4.8%; $P < 0.001$). A significantly greater proportion of patients receiving triple therapy achieved an HbA_{1c} <7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; $P < 0.001$). No difference was observed between combination therapy with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>glimepiride 4 to 8 mg daily</p> <p>vs</p> <p>glimepiride 4 to 8 mg daily, metformin 1,500 to 3,000 mg daily, and placebo</p> <p>vs</p> <p>glimepiride 4 to 8 mg daily plus placebo</p>				<p>glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; $P<0.638$).</p> <p>Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; $P<0.001$).</p> <p>Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported).</p> <p>A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; $P<0.001$). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and quantitative insulin sensitivity check index between the treatments.</p> <p>Sitagliptin significantly increased fasting insulin compared to placebo (1.8 vs 0.1 μIU/mL; $P<0.001$).</p> <p>Sitagliptin was well tolerated, both in combination with glimepiride and in triple therapy. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed with sitagliptin compared to placebo, with the majority of that difference due to rates of minor to moderate hypoglycemia.</p> <p>A significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted with sitagliptin compared to a slight decrease in weight with placebo (-0.4 kg; 95% CI, -0.8 to 0.1).</p>
<p>Rigby et al.⁷⁷ (2010)</p> <p>Rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy)</p> <p>vs</p>	<p>OL</p> <p>Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control (HbA_{1c} 6.5% to 10.0% on a stable</p>	<p>N=169</p> <p>16 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 16</p> <p>Secondary: Change in HbA_{1c} from baseline to week 8, change in FPG and fasting</p>	<p>Primary: At week 16, HbA_{1c} was reduced from baseline in all treatment groups (LS mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; $P=0.031$); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; $P<0.001$); sitagliptin -0.4% (95% CI, -0.64 to -0.13; $P=0.009$).</p> <p>Secondary: At week 8, HbA_{1c} was reduced from baseline with colesevelam and sitagliptin (-0.3%; $P=0.006$ and -0.5%; $P<0.001$, respectively), but not with rosiglitazone (-0.2%; $P=0.109$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>sitagliptin 100 mg QD and metformin (existing therapy)</p> <p>vs</p> <p>colesevelam 3.75 g daily (QD or BID) and metformin (existing therapy)</p>	<p>regimen of metformin (1,500-2,550 mg daily), with LDL-C \geq60 mg/dL and TGs <500 mg/dL</p>		<p>insulin from baseline to weeks 8 and 16, change in 2-hour PPG and postprandial insulin after a meal tolerance test, change in lipid parameters, percentage of participants who achieved an HbA_{1c} reduction >0.7% from baseline, percentage of participants who achieved HbA_{1c} <7.0%</p>	<p>FPG was significantly reduced from baseline at week 8 and week 16 in all treatment groups.</p> <p>The 2-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups.</p> <p>There was no significant change in fasting insulin or 2-hour postprandial insulin from baseline to week 16 in any treatment group.</p> <p>Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008).</p> <p>LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011).</p> <p>TC levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median TG levels increased significantly from baseline with colesevelam (P<0.001) and rosiglitazone (P<0.001); however, sitagliptin did not significantly affect TG levels. HDL-C levels did not change significantly from baseline with any treatment.</p> <p>At week 16, 23.2% of patients in the colesevelam group, 48.1 % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in HbA_{1c} of 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved HbA_{1c} <7.0%.</p> <p>The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				severity.
<p>Douek et al.⁷⁸ (2005)</p> <p>Metformin titrated to 2 grams daily</p> <p>vs</p> <p>placebo</p> <p>All patients received insulin regimens.</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≤ 75 years of age with type 2 diabetes for ≥ 2 years starting insulin due to inadequate glycemic control on oral agents</p>	<p>N=183</p> <p>1 year</p>	<p>Primary: Change in baseline weight</p> <p>Secondary: Changes in baseline HbA_{1c}, insulin dose, frequency of hypoglycemia, treatment satisfaction, well-being from baseline</p>	<p>Primary: Metformin was associated with less weight gain than placebo (mean, 6.1 vs 7.6 kg; adjusted difference, 1.5 kg; 95% CI, 0.2 to 2.9; P=0.02).</p> <p>Secondary: Metformin was associated with a greater decrease in HbA_{1c} (1.5 vs 1.3%; adjusted difference, 0.5%; 95% CI, 0.1 to 0.9%; P=0.02), and a lower insulin requirement (62 vs 86 units; adjusted difference, 25 units; 95% CI, 15 to 34; P<0.001) compared to placebo.</p> <p>Severe hypoglycemia was reported in 10 patients (13%) taking metformin and in one patient (1%) taking placebo (RR, 9.48; 95% CI, 1.24 to 72.2; P=0.009).</p> <p>Treatment satisfaction improved more in patients on metformin than on placebo (P<0.001) as did the positive-well-being score (P=0.02).</p>
<p>Wulffelé et al.⁷⁹ (2002)</p> <p>Metformin 850 to 2,250 mg daily</p> <p>vs</p> <p>placebo</p> <p>All patients received insulin regimens.</p>	<p>DB, PC, RCT</p> <p>Patients 30 to 80 years of age with type 2 diabetes who had received a diagnosis of diabetes after the age of 25, who had experienced no episodes of ketoacidosis, and whose past blood-glucose lowering treatments consisted of oral agents but now consisted of insulin or a combination of insulin and</p>	<p>N=390</p> <p>16 weeks interim analysis</p>	<p>Primary: Changes in HbA_{1c}, insulin requirements, body weight, BMI, BP, and plasma lipids</p> <p>Secondary: Not reported</p>	<p>Primary: Mean HbA_{1c} was 6.94% for metformin and 7.6% for placebo (P<0.0001).</p> <p>Mean daily glucose level decreased from 8.8\pm2.1 to 8.5\pm1.7 mmol/L in the placebo group (mean decrease, -0.16; 95% CI, -0.53 to 0.22 mmol/L) and from 8.8\pm2.2 to 7.8\pm1.7 mmol/L in the metformin group (mean decrease, -1.04; 95% CI, -1.5 to 0.52 mmol/L; P=0.006 vs placebo).</p> <p>Mean insulin requirements were significantly different for metformin (63.8 IU) as compared to placebo (71.3 IU; P<0.0001).</p> <p>Mean weight reduction was significant for metformin (-0.4 kg) as compared to placebo (1.2 kg; P<0.01). BMI increased by 0.4\pm2 kg in the placebo group and decreased by 0.2\pm0.9 kg in the metformin group (P=0.01 vs placebo).</p> <p>There was a small increase in mean SBP and DBP in both groups, but the difference was not significant between the groups (P=0.87 for SBP and P=0.92 for DBP).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	metformin			<p>In the placebo group, mean plasma TC and LDL-C concentrations decreased by -0.04 mmol/L (95% CI, -0.15 to 0.07) and -0.02 mmol/L (95% CI, -0.16 to 0.06), respectively. In the metformin group, mean plasma TC and LDL-C concentrations decreased by -0.25 mmol/L (95% CI, -0.35 to -0.15) and -0.21 mmol/L (95% CI, -0.33 to -0.15), respectively (P<0.01 vs placebo for both).</p> <p>Changes in plasma HDL-C and TG concentrations were not significant in either group.</p> <p>Mild and transient gastrointestinal complaints were reported more frequently in the metformin group (56%) as compared to the placebo group (13%; P<0.0001).</p> <p>Secondary: Not reported</p>
<p>Yki-Järvinen et al.⁸⁰ (2006)</p> <p>Bedtime insulin glargine plus metformin (G+MET)</p> <p>vs</p> <p>bedtime NPH plus metformin (NPH+MET)</p> <p>Initial bedtime doses were 10 units for patients who were previously on metformin alone</p>	<p>MC, OL, PG, RCT</p> <p>Men and women 35 to 75 years of age with type 2 diabetes previously treated with a stable dose of sulfonylurea and metformin (>1.5 g) or metformin alone for at least 3 months prior to screening, with a BMI 20 to 40 kg/m², HbA_{1c} ≥8.0%, FPG ≥7 mmol/L measured during self monitoring of blood glucose between 4 and 2 weeks prior to</p>	<p>N=110</p> <p>36 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Diurnal glucose concentrations, symptomatic hypoglycemia</p>	<p>Primary: At 36 weeks, HbA_{1c} decreased from 9.13±0.15% to 7.14±0.12% and from 9.26±0.15% to 7.16±0.14% in the G+MET and NPH+MET groups, respectively. The changes in HbA_{1c} were determined to be not significant between groups (P value not reported).</p> <p>Secondary: The diurnal profiles were consistently lower in the G+MET group compared to the NPH+MET group (8.6±0.3 vs 10.1±0.3 mmol/L, respectively; P=0.002).</p> <p>During the first 12 weeks, the G+MET group had significantly lower number of episodes of symptomatic hypoglycemia than the NPH+MET group, but the rates became similar thereafter. The frequency of hypoglycemia averaged 5.4 and 8.0 episodes/patient-year for the G+MET and NPH+MET groups, respectively (P=0.12).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>and 20 units for patients who were previously on both metformin and a sulfonylurea.</p> <p>All sulfonylurea medications were discontinued according to the study protocol.</p> <p>Insulin doses were titrated to achieve an FPG 72 to 100 mg/dL in both groups.</p>	<p>study start, and fasting C-peptide ≥ 0.33 nmol/L</p>			
<p>Horton et al.⁸¹ (2000)</p> <p>Nateglinide 120 mg TID before each meal plus metformin 500 mg TID immediately after the start of each meal</p> <p>vs</p> <p>nateglinide 120 mg TID before each meal</p> <p>vs</p>	<p>DB, PC, PRO, RCT</p> <p>Patients ≥ 30 years of age with type 2 diabetes for ≥ 3 months with a BMI 20 to 35 kg/m², and all patients needed to have been treated with diet alone with an HbA_{1c} 6.8 to 11.0% and FPG level ≤ 15 mmol/L</p>	<p>N=701</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c}, FPG, glucose AUC after Sustacal challenge from baseline</p> <p>Secondary: Not reported</p>	<p>Primary: Adjusted mean change from baseline in HbA_{1c}, FPG, and glucose AUC after Sustacal challenge were significantly reduced from baseline ($P \leq 0.0001$) in patients receiving active treatment.</p> <p>HbA_{1c}, FPG, and glucose AUC were all significantly reduced compared to placebo ($P \leq 0.001$), except from glucose AUC with metformin monotherapy.</p> <p>The decrease in HbA_{1c} was greater for metformin compared to nateglinide, the between group difference was small (0.3% difference; $P \leq 0.01$).</p> <p>The decrease in FPG was greater with the metformin group compared to the nateglinide group, the between group difference was 0.9 mmol/L ($P < 0.001$).</p> <p>The combination of nateglinide plus metformin was additive (HbA_{1c}, -1.4% and FPG, -2.4 mmol/L; $P \leq 0.01$ vs either monotherapy).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 500 mg TID immediately after the start of each meal vs placebo				After a Sustacal challenge, there was a greater reduction in mealtime glucose with nateglinide compared to metformin or placebo ($AUC_{0-130 \text{ min}}$, -2.1, -1.1, and 0.6 mmol/hr/L, respectively; $P \leq 0.0001$). A greater reduction was seen with nateglinide plus metformin ($AUC_{0-130 \text{ min}}$, -2.5 mmol/hr/L; $P \leq 0.0001$ vs metformin and placebo). Secondary: Not reported
Marre et al. ⁸² (2002) Metformin 1,000 mg BID and nateglinide 60 to 120 mg TID before meals vs metformin 1,000 mg BID and placebo	DB, MC, PG, RCT Patients ≥ 30 years of age with type 2 diabetes for ≥ 6 months with HbA_{1c} 6.8 to 11.0%, BMI 20 to 35 kg/m ² , and were treated with metformin for a minimum of 3 months and stabilized at a dose of $\geq 1,500$ mg/day for ≥ 4 weeks prior to study entry	N=467 24 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Change in FPG, body weight, and lipid profile (TC, fasting TGs, LDL-C, HDL-C)	Primary: Mean HbA_{1c} was reduced significantly from baseline when compared to the placebo group for the nateglinide 60 mg group (-0.36%; 95% CI, -0.59 to -0.13; $P=0.003$) and for the nateglinide 120 mg group (-0.51%; 95% CI, -0.82 to -0.36; $P < 0.001$) at end point. Dose-dependent reduction in HbA_{1c} was seen with nateglinide irrespective of baseline parameters, with larger mean reductions seen with nateglinide 120 mg. There was little or no change in HbA_{1c} at end point in the placebo group. Secondary: There were modest changes from baseline in FPG in the nateglinide groups and an increase was seen in the placebo group, the difference compared to baseline was significant in both the nateglinide 60 and 120 mg groups ($P=0.044$ and $P=0.003$, respectively). There were no notable changes in body weight at end point in the patients that received placebo (0.1 kg) or nateglinide 60 mg (0.4 kg). There was a significant increase ($P < 0.001$) in mean weight of 0.9 kg in the nateglinide 120 mg group as compared to baseline. Fasting TGs were significantly reduced in the nateglinide 120 mg group as compared to the placebo group at end point ($P=0.042$). The mean changes in TC, LDL-C, and HDL-C remained almost unchanged throughout the study.
Raskin et al. ⁸³ (2003)	MC, OL, PG, RCT Patients ≥ 18 years	N=192 16 weeks	Primary: Final HbA_{1c} values and changes in	Primary: Mean HbA_{1c} changes from baseline were significantly greater in the repaglinide group compared to the nateglinide group (-1.28 vs -0.67%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Metformin 1,000 mg BID and nateglinide 120 mg TID before meals</p> <p>vs</p> <p>metformin 1,000 mg BID and repaglinide 1 to 4 mg TID before meals</p>	<p>of age with type 2 diabetes for ≥ 3 months, BMI 24 to 42 kg/m², HbA_{1c} 7.0 to 12.0% on previous monotherapy with a sulfonylurea, metformin, or low dose glyburide plus metformin</p>		<p>HbA_{1c} from baseline</p> <p>Secondary: Changes in FPG and assessment of glucose area under the time concentration curves from 0 to 240 minutes (AUC_{0-240 min}), insulin AUC_{0-240 min}, and glucagon AUC_{0-240 min} after a liquid test meal at baseline and at study end point</p>	<p>P<0.001).</p> <p>The final HbA_{1c} at 16 weeks was 7.1±1.1% for the repaglinide group and 7.5±1.4% for the nateglinide group.</p> <p>The percent of patients who achieved final HbA_{1c} values $\leq 7.0\%$ was 59% for the repaglinide group and 47% for the nateglinide group (P value not reported).</p> <p>Secondary: FPG values were significantly different between the two treatment groups with one week of therapy. Mean changes in FPG values from baseline were significantly greater for the repaglinide group (-39 vs -21 mg/dL for nateglinide group; P=0.002). The final FPG at 16 weeks was 150.0±45.1 mg/dL for the repaglinide group and 170±52 mg/dL for the nateglinide group. At the end of the 16 week maintenance study, 48% of the repaglinide group had reductions of FPG values >40 mg/dL and 26% of the nateglinide group had a response of this magnitude.</p> <p>Mean end point reductions in PPG levels from baseline were not significantly different between the groups (glucose AUC_{0-240 min}). The treatments were also similar for changes in insulin AUC_{0-240 min} and glucagon AUC_{0-240 min} during the study (P values not reported).</p> <p>There were no patients in either group who experienced major hypoglycemic episodes (requiring the assistance of another person).</p> <p>The most frequent adverse event in both groups was upper respiratory infection (12 vs 21%). Adverse events that occurred from 3 to 8% included nausea, viral infection, accidental injury, sinusitis, diarrhea, and headache. The repaglinide group had 5% incidence of chest pain and arthralgia, as compared to 1% for each in the nateglinide groups. Mean changes from baseline in weight were small for both groups, 0.6 kg gain for repaglinide compared to 0.5 kg loss with nateglinide.</p>
<p>Gerich et al.⁸⁴ (2003) PRESERVE-β</p>	<p>DB, MC, RCT</p> <p>Men and women 18</p>	<p>N=428</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p>	<p>Primary: Both treatments maintained similar reductions in HbA_{1c}. The mean change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Study</p> <p>Metformin 500 to 2,000 mg daily plus nateglinide 120 mg TID</p> <p>vs</p> <p>metformin 500 to 2,000 mg daily plus glyburide 1.25 to 10 mg daily</p>	<p>to 77 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤15 mmol/L, BMI 22 to 45 kg/m² and inadequately controlled on diet and exercise</p>		<p>(average of weeks -2 and 0) to week 104</p> <p>Secondary: Change from baseline to week 104 in FPG, body weight, AUC_{0-120 min} of glucose during oral glucose tolerance tests</p>	<p>group (-1.2±0.1%) was similar (P=0.1730) to that in the glyburide plus metformin group (-1.5±0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.0001) after one and two years of treatment and there was no significant difference between the groups.</p> <p>Secondary: Mean change in FPG was -1.6±0.2 mmol/L in patients in the nateglinide plus metformin group (P<0.0001 vs baseline) and -2.4±0.2 mmol/L in patients in the glyburide plus metformin group (P<0.0001 vs baseline; P=0.0078 vs nateglinide plus metformin).</p> <p>Body weight decreased in the nateglinide plus metformin group (-0.4±0.4 kg) and increased in the glyburide plus metformin group (0.8±0.5 kg). The change from baseline was significant for the glyburide plus metformin group (P=0.0011) only (P=0.8413 for the nateglinide plus metformin group). The difference between groups was statistically significant (P=0.0115).</p> <p>No data was reported for AUC of glucose during oral glucose tolerance tests.</p>
<p>Schwarz et al.⁸⁵ (2008)</p> <p>Metformin 2,000 mg QD and nateglinide 120 mg TID before meals</p> <p>vs</p> <p>metformin 2,000 mg QD and glyburide 10 mg QD</p>	<p>AC, DB, MC, RCT</p> <p>Men and women ≥65 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤15 mmol/L, BMI of 22 to 45 kg/m²</p>	<p>N=69</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Change from baseline to week 104 in FPG, two-hour PPG using the incremental AUC (AUC_{0-120 min}) of glucose during oral glucose tolerance tests, the proportion of patients achieving a target HbA_{1c} <7.0</p>	<p>Primary: Similar reductions in HbA_{1c} were seen with both treatments. The average change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (-1.2±0.2%) was similar (P=0.310) to that in the glyburide plus metformin group (-1.2±0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.001) after two years of treatment and there was no significant difference between the groups.</p> <p>Secondary: Mean change in FPG was -26±6 mg/dL in patients receiving nateglinide plus metformin (P<0.001 vs baseline) and -36±6 mg/dL in patients receiving glyburide plus metformin (P<0.001 vs baseline) (P=0.234 between the groups).</p> <p>There was no significant changes in two-hour PPG from baseline for nateglinide plus metformin glyburide plus metformin groups (-15±7</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			or $\leq 6.5\%$, adverse events	<p>mg/dL; $P=0.071$ and -8 ± 8 mg/dL; $P=0.385$, respectively).</p> <p>The proportion of patients who achieved a target $HbA_{1c} < 7.0\%$ in the nateglinide plus metformin group was not significantly different compared to the glyburide plus metformin group (70 vs 65%, respectively; $P=0.736$).</p> <p>Similar proportions of patients in the nateglinide plus metformin group and the glyburide plus metformin group maintained a target HbA_{1c} of $\leq 6.5\%$ (40 and 60%, respectively; $P=0.206$).</p> <p>Approximately 94% of patients in the nateglinide plus metformin group and 88% of patients in the glyburide plus metformin group reported one or more adverse events. One mild hypoglycemic event occurred with nateglinide plus metformin treatment vs 8 mild-to-severe hypoglycemic events with glyburide plus metformin treatment ($P<0.023$).</p>
<p>Derosa et al.⁸⁶ (2009)</p> <p>Metformin 1,500 to 3,000 mg daily plus nateglinide 60 mg TID</p> <p>vs</p> <p>metformin 1,500 to 3,000 mg daily plus glyburide 7.5 to 12.5 mg daily</p>	<p>DB, MC, PG, RCT</p> <p>Patients ≥ 18 years of age with type 2 diabetes, $HbA_{1c} > 7.0\%$, BMI 25 to 28 kg/m², and hypertensive (SBP/DBP, $>130/\geq 85$ mmHg)</p>	<p>N=248</p> <p>12 months</p>	<p>Primary:</p> <p>Changes in BMI, FPG and PPG, HbA_{1c}, fasting and postprandial plasma insulin, HOMA index, and lipid profile, BP</p>	<p>Primary:</p> <p>BMI did not show any significant change during the study.</p> <p>A significant reduction in HbA_{1c} was shown after 9 months ($P<0.05$) and 12 months ($P<0.01$) in the nateglinide group compared to the baseline value. A significant reduction in HbA_{1c} was seen with glyburide after 12 months ($P<0.05$) compared to baseline. The HbA_{1c} at 12 months was 6.4% in the nateglinide group compared to 7.3% in the glyburide group ($P<0.05$).</p> <p>After nine and 12 months, mean FPG levels were significantly decreased in the nateglinide and glyburide groups ($P<0.05$ and $P<0.01$, respectively) compared to baseline.</p> <p>Significant changes in PPG were found at nine months ($P<0.05$) in the nateglinide group and after 12 months in glyburide and nateglinide groups ($P<0.05$ and $P<0.01$, respectively) compared to baseline.</p> <p>Fasting plasma insulin and postprandial plasma insulin did not show any significant change after three, six, nine and 12 months in both groups compared to the baseline.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>HOMA index decrease was obtained only at 12 months ($P<0.05$) compared to the baseline value in both groups,</p> <p>No significant change was observed in TC, LDL-C, HDL-C, TG, Apo A-I, Apo B, SBP, DBP and heart rate in either group after three, six, nine and 12 months.</p>
<p>Wang et al. (abstract)⁸⁷ (2011)</p> <p>Repaglinide 1 mg TID, titrated up to 4 mg TID</p> <p>vs</p> <p>repaglinide 1 mg TID plus metformin 500 mg TID, titrated up to 4 mg TID and 500 mg TID</p>	<p>AC, OL, PG, RCT</p> <p>Patients 18 to 75 years of age with type 2 diabetes, $HbA_{1c} >8.5\%$, $BMI \leq 35 \text{ kg/m}^2$, and who were naïve to oral antidiabetic agents,</p>	<p>N=432</p> <p>16 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, two-hour PPG, seven-point plasma glucose, safety</p>	<p>Primary: Mean HbA_{1c} reduction was $4.51 \pm 1.64\%$ with combination therapy and $4.05 \pm 1.59\%$ with repaglinide. Estimated mean treatment difference for combination therapy vs repaglinide was -0.30% (95% CI, -0.49 to -0.11; $P < 0.01$).</p> <p>Secondary: Combination therapy demonstrated significant improvements compared to repaglinide in FPG, seven-point plasma glucose, and lunchtime and dinnertime two-hour PPG ($P < 0.05$ for all).</p> <p>Hypoglycemia rates were 2.04 events/patient-year with combination therapy compared to 1.35 events/patient-year with repaglinide ($P=0.058$). Adverse events were comparable between the two treatments.</p>
<p>Moses et al.⁸⁸ (1999)</p> <p>Repaglinide 0.5 to 4 mg TID before each meal plus metformin 1,000 to 3,000 mg/day</p> <p>vs</p> <p>repaglinide 0.5 to 4 mg TID before each meal</p>	<p>DB, MC, PG, RCT</p> <p>Patients 40 to 75 years of age with type 2 diabetes treated with metformin alone (1 to 3 g/day) for >6 months and had not achieved optimal glycemic control ($HbA_{1c} >7.0\%$) and $BMI \geq 21 \text{ kg/m}^2$</p>	<p>N=83</p> <p>3 months</p>	<p>Primary: Change in baseline HbA_{1c} and FPG</p> <p>Secondary: Change in fasting insulin, C-peptide levels, fasting TG, TC, HDL-C, LDL-C, FFA, body weight</p>	<p>Primary: Patients in the metformin plus repaglinide group had a significant decrease in HbA_{1c} from 8.3 to 6.9% ($P=0.0016$) and FPG from 10.2 to 8.0 mmol/L ($P=0.0003$) compared to baseline. There were no significant changes in HbA_{1c} or FPG for patients receiving metformin alone and repaglinide alone. The HbA_{1c} and FPG changes from baseline for metformin plus repaglinide vs metformin alone and metformin plus repaglinide vs repaglinide were significant ($P < 0.05$ for all).</p> <p>Secondary: Fasting insulin and C-peptide levels increased significantly from baseline in both groups receiving repaglinide ($P < 0.05$ for both).</p> <p>Lipid levels (TC, HDL-C, LDL-C, TG, FFA) did not change significantly from baseline in the metformin plus repaglinide group. No significant</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metformin 1,000 to 3,000 mg/day				differences were found between the metformin plus repaglinide group and the monotherapy groups. In both groups receiving repaglinide there was an increase in body weight which was significant compared to baseline (P<0.05 for both).
Civera et al. ⁸⁹ (2008) Metformin 850 mg BID, repaglinide 2 mg TID before meals, and NPH insulin before dinner vs metformin 850 mg BID and NPH insulin before dinner vs NPH insulin BID	OL, PG Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs	N=37 24 weeks	Primary: HbA _{1c} , hypoglycemia, body weight Secondary: Not reported	Primary: The HbA _{1c} was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; P=0.02) and the NPH insulin group (8.4%; P=0.02). The absolute reduction in HbA _{1c} was -2.4% in the repaglinide triple therapy group compared to -0.7% (P=0.01) in the metformin plus NPH insulin group and -1.4% in the insulin NPH group. Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (P<0.01). Significant differences in weight gain and hypoglycemia were not seen. Secondary: Not reported
Black et al. ⁹⁰ (2007) Meglitinide vs meglitinide plus metformin vs	MA (15 trials) Patients with type 2 diabetes	N=3,781 Duration varied	Primary: Mortality and morbidity Secondary: Change in HbA _{1c} , weight or BMI, hypoglycemia, adverse effects, quality of life	Primary: No trials reported the effect of meglitinides on mortality and morbidity. Secondary: In the 11 trials comparing meglitinides to placebo, both repaglinide and nateglinide resulted in reductions in HbA _{1c} (0.1 to 2.1% and 0.2 to 0.6%, respectively). In two trials comparing repaglinide to nateglinide, reduction in HbA _{1c} was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in HbA _{1c} compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in HbA _{1c} compared to metformin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>meglitinide plus insulin</p> <p>vs</p> <p>metformin</p> <p>vs</p> <p>placebo</p>				<p>Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin.</p> <p>Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides.</p> <p>There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes.</p> <p>There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization Diabetes Treatment Satisfaction Questionnaire improved significantly in patients receiving repaglinide compared to patients receiving placebo.</p>
<p>Bayraktar et al.⁹¹ (1996)</p> <p>Metformin 500 mg TID and sulfonylurea</p> <p>vs</p> <p>acarbose 50 to 100 mg TID and sulfonylurea</p>	<p>RCT, XO</p> <p>Patients from 30 to 63 years of age with type 2 diabetes for 2 to 20 years, HbA_{1c} >8.5%, FPG >7.7 mmol/L, or a PPG>10 mmol/L on maximum doses of gliclazide† (240 mg daily)</p>	<p>N=18</p> <p>20 weeks</p>	<p>Primary: Changes in FPG, PPG, HbA_{1c}, TG, cholesterol, fibrinogen, insulin levels, and C-peptide levels from baseline</p> <p>Secondary: Not reported</p>	<p>Primary: Mean FPG, PPG, and HbA_{1c} decreased at the end of each combination treatment period as compared with baseline levels (P<0.05).</p> <p>PPG level in the acarbose group was lower than the level achieved by the group using metformin (P<0.05).</p> <p>There was a significant decrease between pre- and posttreatment two-hour PPG levels in each group (-5.3±0.4 for acarbose vs -2.9±0.3 for metformin, P<0.05).</p> <p>There were small reductions in fibrinogen, insulin, and C-peptide levels in each group, but the differences were not statistically significant.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
<p>Abbasi et al.⁹² (2004)</p> <p>Metformin 500 to 1,000 mg BID added to existing sulfonylurea monotherapy</p> <p>vs</p> <p>metformin 500 to 1,000 mg BID added to existing dietary therapy</p>	<p>RCT</p> <p>Patients with type 2 diabetes with relatively poor glycemic control with FPG >9.5 mmol/L on dietary therapy alone or sulfonylurea monotherapy, BMI <40 kg/m², and no apparent cardiovascular disease</p>	<p>N=31</p> <p>12 weeks</p>	<p>Primary: Changes in fasting glucose, HbA_{1c}, lipid concentrations</p> <p>Secondary: Not reported</p>	<p>Primary: FPG decreased to a similar degree with diet therapy (metformin) (12.45±0.48 vs 9.46±0.47 mmol/L; P<0.001) and combined sulfonylurea plus metformin (14.09±0.51 vs 10.57±0.85 mmol/L; P=0.001). The changes in the diet therapy (metformin) group compared to the combined sulfonylurea plus metformin group was not significant (P=0.58).</p> <p>Changes in fasting HbA_{1c} from baseline were significant for diet therapy (metformin) (P<0.001) and combined sulfonylurea plus metformin (P<0.002). The changes were not significant when compared to each other (P=0.30).</p> <p>Fasting TC, TG, HDL-C, and LDL-C did not change significantly in either treatment group (P=0.64, P=0.34, P=0.48, and P=0.85, respectively) for diet therapy (metformin) compared to combined sulfonylurea plus metformin.</p> <p>Fasting remnant lipoprotein cholesterol concentrations were significantly lower in the diet therapy (metformin) group as compared to baseline (0.43±0.09 vs 0.34±0.07 mmol/L; P=0.02). The changes were not significant for diet therapy (metformin) compared to combined sulfonylurea plus metformin (P=0.06).</p> <p>Concentrations of FFA and remnant lipoprotein cholesterol concentrations were lower to a similar degree in both groups, whereas day long plasma insulin concentrations were unchanged. Changes in LDL particle diameter and percent of small dense LDL particles between the groups were not significant at end point (P=0.28 and P=0.73, respectively).</p> <p>Secondary: Not reported</p>
<p>DeFronzo et al.⁹³ (1995)</p> <p><u>Protocol 1:</u></p>	<p>2 DB, PG, RCT</p> <p>Moderately obese patients with type 2</p>	<p><u>Protocol 1</u></p> <p>N=289</p> <p>29 weeks</p>	<p>Primary: Changes in plasma glucose, HbA_{1c}, plasma insulin,</p>	<p>Primary: <u>Protocol 1:</u> As compared to the placebo group, the metformin group had lower mean FPG concentrations (189±5 vs 244±6 mg/dL; P<0.001). HbA_{1c} levels were</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Metformin 850 to 2,550 mg daily</p> <p>vs</p> <p>placebo</p> <p><u>Protocol 2:</u> Metformin plus glyburide</p> <p>vs</p> <p>metformin 500 to 2,500 mg daily</p> <p>vs</p> <p>glyburide 5 to 10 mg BID</p>	<p>diabetes inadequately controlled by diet (Protocol 1) or diet plus glyburide (Protocol 2)</p>	<p><u>Protocol 2</u> N=632 29 weeks</p>	<p>lipids, plasma lactate</p> <p>Secondary: Not reported</p>	<p>also lower in the metformin group (7.1±0.1 vs 8.6±0.2%; P<0.001).</p> <p>The changes from baseline for TC and LDL-C for metformin were significant compared to placebo (P=0.001 and P=0.019, respectively).</p> <p>Fasting plasma lactate levels were similar at all times during the active-treatment in both groups.</p> <p><u>Protocol 2:</u> Patients in the metformin plus glyburide combination group, compared to the glyburide alone group, had lower mean FPG concentrations (187±4 vs 261±4 mg/dL; P<0.001), and HbA_{1c} values (7.1±0.1 vs 8.7±0.1%; P<0.001). The effect of metformin alone was similar to that of glyburide alone.</p> <p>The changes from baseline were significant compared to glyburide for the following: TC, metformin (P=0.011) and metformin plus glyburide (P=0.001); LDL-C, metformin (P=0.009) and metformin plus glyburide (P=0.001); and TG, each glyburide and metformin plus glyburide (P=0.001)</p> <p>Fasting plasma lactate did not change in any of the groups in the course of treatment.</p> <p>Secondary: Not reported</p>
<p>Goldstein et al.⁹⁴ (2003)</p> <p>Metformin 500 to 2,000 mg daily</p> <p>vs</p> <p>glipizide 15 mg BID</p>	<p>DB, MC, PG, RCT</p> <p>Patients with type 2 diabetes and inadequate glucose control (HbA_{1c} 7.5 to 12.0%) despite monotherapy with at least half the maximum labeled daily dose of a</p>	<p>N=247</p> <p>18 weeks</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: Changes in FPG, three-hour PPG, area under the concentration-time curve (AUC), three-hour postprandial</p>	<p>Primary: The decreases in HbA_{1c} were significantly greater in the glipizide/metformin group compared to either of the monotherapy groups (P<0.001). A total of 36.6% of patients receiving glipizide/metformin, 8.9% of patients receiving glipizide, and 9.9% of patients receiving metformin had an HbA_{1c} <7.0% at the final visit.</p> <p>Secondary: Combination therapy reduced the FPG from baseline significantly more compared to glipizide and metformin monotherapies (P<0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>glipizide/ metformin 5/500 mg daily (dose titrated up to 4 tablets per day)</p>	<p>sulfonylurea, FPG <300 mg/dL, and BMI ≥25 to ≤40 kg/m²</p>		<p>insulin incremental AUC during three hours after a standard test meal, fasting insulin level, serum lipid profiles, body weight</p>	<p>Combination therapy controlled PPG more than metformin monotherapy or glipizide monotherapy, as measured using a three-hour incremental AUC (P=0.002, and P<0.001, respectively).</p> <p>The postprandial insulin three-hour incremental AUC increased from baseline with combination therapy, and decreased with glipizide monotherapy; the differences between these groups were not significant. There was a decrease in the postprandial insulin AUC in the metformin monotherapy group, which was significant (P<0.001 vs combination group).</p> <p>Fasting insulin decreased in the combination therapy group and in the metformin monotherapy group. Fasting insulin increased in the glipizide monotherapy group. The changes in the combination therapy group did not differ significantly from either monotherapy group.</p> <p>There were decreases in body weight in all groups, -0.3 kg with the combination therapy group, -0.4 kg with the glipizide monotherapy group, and -2.7 kg in the metformin monotherapy group. The changes in the metformin monotherapy group were significant compared to the combination therapy group (P<0.001).</p> <p>There were no significant changes in the fasting lipid profile in the combination group or metformin monotherapy group. There were significant increases from baseline in TC and TG in the glipizide monotherapy group.</p>
<p>Garber et al.⁹⁵ (2002)</p> <p>Metformin 500 mg daily</p> <p>vs</p> <p>glyburide 2.5 mg daily</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with type 2 diabetes with inadequate glycemic control with diet and exercise, HbA_{1c} >7.0%, normal renal and liver</p>	<p>N=806</p> <p>20 weeks</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: Changes in FPG, two-hour PPG, fasting and two- hour insulin levels, serum lipid concentrations, body weight</p>	<p>Primary: Patients in both glyburide/metformin groups had significantly greater mean reduction from baseline HbA_{1c} (level of 8.2%) compared to the placebo group (P<0.001). The reductions in HbA_{1c} from baseline for each glyburide/metformin group were significantly greater than the placebo or metformin groups (P<0.001). The reduction in HbA_{1c} in the glyburide/metformin 1.25/250 mg group was significantly greater compared to the glyburide group (P<0.016), and for the glyburide/metformin 2.5/500 mg group compared to the glyburide group (P<0.004).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>glyburide/ metformin 1.25/250 mg daily</p> <p>vs</p> <p>glyburide/ metformin 2.5/500 mg daily</p> <p>vs</p> <p>placebo</p> <p>Doses were titrated to a maximum of 4 tablets per day.</p>	<p>function, and a BMI ≤ 38 kg/m²</p>			<p>Sixty-six percent of the patients in the glyburide/metformin 1.25/250 mg group (P=0.006 vs metformin) and 72% of the patients in the glyburide/metformin 2.5/500 mg group (P<0.001 vs metformin, P=0.037 vs glyburide) had achieved an HbA_{1c} <7.0% compared to 60% of the patients in the glyburide group, 50% of patients in the metformin group, and 20% of patients in the placebo group.</p> <p>Secondary: Mean decreases in FPG concentrations were significantly greater for both combination groups compared to the placebo (P<0.001) and metformin groups (P<0.001). Mean decreases in FPG were numerically greater in both combination groups compared to the glyburide group, but the differences were not significant.</p> <p>Glyburide/metformin 1.25/250 mg group, glyburide/metformin 2.5/500 mg group, and the glyburide group had modest changes in body weight of 1.4, 1.9, and 1.7 kg, respectively, compared to 0.7 and 0.6 kg mean decrease in patients receiving placebo and metformin, respectively. The mean changes in body weight for the glyburide/metformin groups and the glyburide group were significantly different from placebo.</p> <p>There were no significant changes seen in TC, LDL-C, or HDL-C, and TGs with any treatment.</p>
<p>Marre et al.⁹⁶ (2002)</p> <p>Metformin 500 mg daily</p> <p>vs</p> <p>glyburide 5 mg daily</p> <p>vs</p> <p>glyburide/</p>	<p>DB, MC, PG, RCT</p> <p>Patients >18 years of age with type 2 diabetes with a FPG ≥ 126 mg/dL despite treatment with monotherapy metformin ≥ 850 mg BID or ≥ 500 mg TID, diet, and exercise for 2 months prior to enrollment, and</p>	<p>N=411</p> <p>16 weeks</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: Changes in FPG, fructosamine levels</p>	<p>Primary: Mean HbA_{1c} levels improved in all groups. There were significantly greater reductions in the patients receiving combination therapy as compared to either monotherapy (P<0.05). There were no significant differences in the amount of the reductions in the HbA_{1c} between the two combination therapies or the two monotherapies.</p> <p>Seventy-five percent of the glyburide/metformin 2.5/500 mg group and 63.8% of the glyburide/metformin 5/500 mg group achieved an HbA_{1c} <7.0% as compared to the metformin (37.6%) or glyburide (41.9%) groups (P=0.001 for both).</p> <p>Secondary: FPG decreased in all groups. There were significant improvements in both</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 2.5/500 mg daily vs glyburide/ metformin 5/500 mg daily Doses were titrated to a maximum of 4 tablets per day.	BMI <40 kg/m ²			the combination groups compared to either monotherapy (P<0.05). There were no significant differences in effects on FPG between either of the combination therapies or the monotherapies. Mean decreases in fructosamine in both combination groups were significantly greater (P<0.05) compared to the changes seen in the monotherapy groups.
Johnson et al. ⁹⁷ (2005) Metformin and sulfonylurea vs metformin monotherapy vs sulfonylurea monotherapy	RETRO Patients ≥30 years of age who were new users of oral antidiabetic drugs (sulfonylurea monotherapy, metformin monotherapy, or combination therapy of sulfonylureas and metformin)	N=4,124 N=2,138 sulfonylurea monotherapy N=923 metformin monotherapy N=1,081 combination therapy Duration not reported	Primary: Composite end point of fatal or nonfatal cardiovascular related events Secondary: Not reported	Primary: A total of 381 patients died from cardiovascular causes and 715 were hospitalized at least once for cardiovascular reasons. Patients in the metformin monotherapy group had the lowest nonfatal hospitalization rate for cardiovascular causes (53.7 hospitalizations per 1,000 person years) compared to sulfonylurea monotherapy patients (75.3 per 1,000 person years; P<0.05) and compared to combination therapy patients (90.2 per 1,000 person years; P<0.05). Nonfatal cardiovascular related hospitalization rates were similar for sulfonylurea monotherapy patients and combination therapy patients (P=0.08). Metformin monotherapy was associated with a lower risk of the composite end point (adjusted HR, 0.81; 95% CI, 0.68 to 0.97) as compared to sulfonylurea monotherapy. Cardiovascular hospitalizations were similar for sulfonylurea monotherapy and combination therapy (P=0.32). Secondary: Not reported
Hollander et al. ⁹⁸ (2015) Insulin glargine+ one oral	MC, OL, RCT Type 2 diabetes patients 18 to 79 years of age with a	N=337 48 weeks	Primary: Change in HbA _{1c} Secondary: Changes in FPG,	Primary: Substitution of insulin glargine for a TZD and addition of a third OAD resulted in an adjusted mean change in HbA _{1c} from baseline of -1.66% and -1.86%, respectively (adjusted mean difference 0.20; 95% CI, -0.11 to 0.51). The upper limit of the 95% CI for the difference in the adjusted

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>antidiabetes drug (metformin or sulfonylurea) wherein previous TZD therapy was dropped and replaced with insulin glargine (GLAR +1 OAD)</p> <p>vs</p> <p>three oral antidiabetes drugs (3OAD) wherein patients receiving TZD and metformin received add-on sulfonylurea (glyburide) and patients receiving TZD and sulfonylurea received add-on metformin (3OAD)</p>	<p>HbA_{1c} of 7.5 to 12.0% despite ≥3 months of treatment with a TZD plus metformin or a sulfonylurea</p>		<p>weight, BMI, and serum lipid profile</p>	<p>mean changes from baseline to endpoint for HbA_{1c} was 0.51%; therefore, the primary efficacy analysis did not demonstrate equivalent glycemic control during treatment with GLAR + 1 OAD and 3OAD as measured by HbA_{1c} levels. In patients originally taking sulfonylurea, there was a significantly greater reduction in HbA_{1c} in those adding metformin to TZD and sulfonylurea versus those switching the TZD for GLAR + SU at weeks 12, 24, and 48.</p> <p>Secondary: Adjusted mean FPG at baseline was similar between the two treatment arms (GLAR + 1 OAD 193.0 mg/dL vs 3OAD 199.5 mg/dL; P=0.4299). FPG reduced significantly from baseline to endpoint (P<0.0001 for both arms).</p> <p>Weight gain was observed in both treatment arms at each study visit and at endpoint. At each visit, patients in the GLAR + 1 OAD arm gained less weight than those in the 3OAD arm; this difference was significant at week 12 (P=0.0035). A similar pattern was observed for BMI.</p> <p>Overall, insulin glargine + metformin was as effective as 3OAD in achieving glycemic control but with greater improvements in lipid parameters, less weight gain, and lower hypoglycemia rates.</p>
<p>Duckworth et al.⁹⁹ (2003)</p> <p>Glyburide/ metformin</p>	<p>RETRO</p> <p>Patients 18 to 80 years of age with type 2 diabetes were eligible if they had received a combination product with glyburide and</p>	<p>N=72</p> <p>196 days (mean follow-up)</p>	<p>Primary: Changes in HbA_{1c}, lipid parameters, weight</p> <p>Secondary: Not reported</p>	<p>Primary: The mean baseline HbA_{1c} in the total population was 8.3±1.7%. The mean reduction in HbA_{1c} was 0.6% (P=0.002) with a mean follow-up of 196 days after the initiation of glyburide/metformin. The mean daily doses of glyburide and metformin at baseline and at final follow-up were 17.2 and 1,607 mg and 14.7 and 1,750 mg, respectively.</p> <p>The greatest decrease in HbA_{1c} was observed in patients with a baseline HbA_{1c} ≥8.0% (n=37). This group had a mean reduction of HbA_{1c} of 1.3% (P=0.0002) with similar doses of glyburide (14.7 vs 16.9 mg; P=0.077)</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	metformin for ≥ 90 days and had been treated with glipizide or glyburide plus metformin for ≥ 6 months prior to switching to the combination product of glyburide/metformin			<p>and metformin (1,743 vs 1,624 mg; $P=0.11$) in both treatment periods.</p> <p>There were no significant changes in TC, HDL-C, LDL-C, or TG from baseline.</p> <p>There were no significant changes in body weight from a baseline level of 104.3 kg to the last follow-up weight of 104.0 kg ($P=0.0645$).</p> <p>There were no significant differences in patient adherence to the regimen (92.4% before vs 90.9% after).</p> <p>Secondary: Not reported</p>
<p>Blonde et al.¹⁰⁰ (2003)</p> <p>Glyburide coadministered with metformin</p> <p>vs</p> <p>glyburide/metformin</p>	<p>RETRO</p> <p>Patients with type 2 diabetes new to the combination product glyburide/metformin or glyburide coadministered with metformin between August 2000 and July 2001 and had HbA_{1c} levels at baseline within 79 to 194 days of initiating combination therapy</p>	<p>N=1,421</p> <p>~ 6 month (follow-up period)</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: Not reported</p>	<p>Primary: The mean HbA_{1c} for the two groups at baseline were similar, 9.1% for the combination product and 9.2% for the individual agents coadministered. During the follow-up period, patients taking the combination product had a lower mean daily dose of glyburide and metformin than patients receiving the individual agents coadministered regardless of baseline HbA_{1c}.</p> <p>Fifty-six percent of patients in the combination group achieved an HbA_{1c} <7.0% compared to 31.2% of patients receiving the individual agents coadministered. The mean HbA_{1c} decrease from baseline in the combination group was -2.02% and -1.49% when the individual agents were coadministered. The regression results indicated that patients taking the combination product had a significantly greater ($P<0.0001$) reduction in HbA_{1c} than patients receiving the individual agents coadministered.</p> <p>Patients receiving the combination product with baseline HbA_{1c} $\geq 8.0\%$ experienced a significantly ($P<0.0001$) greater decrease in HbA_{1c} of 2.93% compared to 1.92% for the individual agents coadministered.</p> <p>For patients with baseline HbA_{1c} <8.0%, the difference between the HbA_{1c} responses remained significant. The reductions in HbA_{1c} were smaller for both the combination product and the individual agents coadministered (-0.54 and -0.23%; $P=0.0017$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Patients were more adherent with the combination product than the individual agents coadministered (84% days with drug supply vs 76% days with drug supply, respectively; $P < 0.0001$). The mean decreases in HbA_{1c} were similar for those patients $\geq 80\%$ adherent and $< 80\%$ adherent for the combination product (2.12 vs 2.19%; P value not significant) and the individual agents coadministered (1.47 vs 1.24%; P value not significant).</p> <p>Secondary: Not reported</p>
<p>Lewin et al.¹⁰¹ (2007)</p> <p>Metformin XR (Glumetza®) 1,500 mg QD, 2,000 mg QD, or 1,000 mg BID and glyburide 15 mg QD</p> <p>vs</p> <p>glyburide 15 mg QD</p>	<p>DB, MC, RCT</p> <p>Type 2 diabetic patients 18 to 79 years of age, drug naïve or previously treated with oral antidiabetic medications (monotherapy with any oral antidiabetic medications up to half the maximum therapeutic dose), HbA_{1c} 7.5 to 12.0% in drug-naïve patients or 6.5 to 12.0% in prior drug treatment patients, FPG 200 to 400 mg/dL (drug naïve patients) or 120 to 250 mg/dL (prior drug treatment patients) and C-peptide levels > 0.8</p>	<p>N=607</p> <p>30 weeks</p>	<p>Primary: Change baseline HbA_{1c}</p> <p>Secondary: Changes in HbA_{1c} and FPG at week eight, fructosamine, TC, HDL-C, LDL-C, TG, weight, BMI, discontinuation rates, adverse events</p>	<p>Primary: There were significant reductions in HbA_{1c} from baseline to week 30 in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (-0.74 vs 0.08%, respectively; $P < 0.001$).</p> <p>Secondary: There were significant reductions from baseline in mean FPG and in mean HbA_{1c} at week eight in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group ($P < 0.001$).</p> <p>There were significant differences between the combined metformin and sulfonylurea groups and the monotherapy group for mean changes in fructosamine, TC, HDL-C, and LDL-C ($P < 0.001$ for all).</p> <p>There were significant increases from baseline in mean weight and BMI in the monotherapy sulfonylurea group ($P < 0.001$). In comparison, there was no significant change in weight and a smaller increase in mean BMI in the combined metformin and sulfonylurea groups ($P = 0.028$).</p> <p>There was a significant difference in the rates of hypoglycemia between groups, which were 11.6% in the combined metformin and sulfonylurea groups and 4.2% in the monotherapy sulfonylurea group ($P = 0.007$). However, no significant difference between these two groups was observed for gastrointestinal events.</p> <p>Forty patients (9.3%) in the combined metformin and sulfonylurea groups</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	ng/mL			and three patients (2.1%) in the monotherapy sulfonylurea group discontinued treatment due to an adverse event, mainly hypoglycemia (P=0.001).
<p>Chien et al.¹⁰² (2007)</p> <p>Metformin 500 mg BID</p> <p>vs</p> <p>glyburide 5 mg BID</p> <p>vs</p> <p>glyburide/ metformin 2.5/500mg BID</p> <p>vs</p> <p>glyburide/ metformin 5/500 mg BID</p> <p>The doses were titrated every 2 weeks to a maximum of 4 tablets per day if the exceeded 140 mg/dL.</p>	<p>DB, MC, PG, RCT</p> <p>Patients 30 to 75 years of age with type 2 diabetes, BMI 18.5 to 35.0 kg/m², FPG 140 to 250 mg/dL, and HbA_{1c} 7.0 to 12.0% at the screening visit and FPG ≥140 mg/dL at the second visit, maintained stable sulfonylurea regimen, with or without metformin use</p>	<p>N=100</p> <p>16 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, adverse events</p>	<p>Primary: After 16 weeks, the HbA_{1c} increased in patients receiving glyburide (0.52%; P=0.0018) and there was no change in patients receiving metformin (0.09%; P value not significant).</p> <p>After 16 weeks, treatment with glyburide/metformin 2.5/500 mg resulted in a greater reduction in HbA_{1c} compared to glyburide or metformin (-1.77%; P<0.001 and -1.34%; P=0.002). Treatment with glyburide/metformin 5/500 mg resulted in a greater reduction in HbA_{1c} compared to glyburide or metformin alone (-1.73%; P<0.001 and -1.30%; P=0.005).</p> <p>After 16 weeks, 19 and 24% of patients in the glyburide/metformin groups (2.5/500 mg and 5/500 mg, respectively) had an HbA_{1c} <7.0% compared to 12.0% in the metformin monotherapy group and 6% in the glyburide monotherapy group.</p> <p>Secondary: Mean changes in FPG from baseline were -43 mg/dL in the glyburide group, -41 mg/dL in the metformin group, -98 mg/dL in the glyburide/metformin 2.5/500mg group, and -101 mg/dL in the glyburide/metformin 5/500 mg group. The two glyburide/metformin groups had significant reductions from baseline compared to the monotherapy groups (P<0.0125 compared to glyburide and metformin).</p> <p>Treatment with glyburide/metformin 2.5/500 mg resulted in a 55 mg/dL reduction in FPG compared to glyburide (P=0.001) and a 57 mg/dL reduction in FPG compared to metformin (P=0.001). Treatment with glyburide/metformin 5/500 mg resulted in a in a 58 mg/dL reduction in FPG compared to glyburide (P<0.001) and a 60 mg/dL reduction in FPG compared to metformin (P=0.001).</p> <p>Ninety-eight episodes of adverse events were reported from the screening visit to the end of the study. Four (14.3%) patients reported adverse events</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>associated with hypoglycemia in the glyburide/metformin 2.5/500 mg group, and two (8.3%) patients reported adverse events associated with gastrointestinal disease among all patients who took metformin during the entire course of the study. The highest incidence of gastrointestinal adverse effects was 32.0% in metformin group, and the lowest was 7.7% in the glyburide/metformin 2.5/500 mg group (P=0.021).</p>
<p>Einhorn et al.¹⁰³ (2000)</p> <p>Metformin (existing therapy)</p> <p>vs</p> <p>metformin (existing therapy) and pioglitazone 30 to 45 mg</p>	<p>DB, PC, RCT</p> <p>Patients with poorly controlled type 2 diabetes (HbA_{1c} ≥8.0%) with metformin monotherapy</p>	<p>N=328</p> <p>16 weeks</p>	<p>Primary: Change in HbA_{1c}, FPG, insulin, lipoproteins, and C-peptide</p> <p>Secondary: Not reported</p>	<p>Primary: Reductions in HbA_{1c} with pioglitazone add-on therapy were significantly lower compared to placebo (-0.83% difference between treatment groups; P≤0.05).</p> <p>Reductions in FPG with pioglitazone add-on therapy were significantly lower compared to placebo (-37.7 mg/dL difference between treatment groups; P≤0.05).</p> <p>Pioglitazone reduced fasting C-peptide levels (-0.1 ng/mL) while placebo increased levels (0.1 ng/mL; P≤0.05).</p> <p>Pioglitazone reduced fasting C-insulin levels (-2.1 ng/mL) while placebo increased levels (0.4 ng/mL; P<0.05).</p> <p>Pioglitazone add-on therapy significantly reduced TG (-9.7 vs 8.5 mg/dL; P≤0.05) and increased HDL-C (10.2 vs 1.5 mg/dL; P≤0.05) compared to placebo.</p> <p>Both treatment groups increased LDL-C (7.7 vs 11.9 mg/dL; P value not significant).</p> <p>No significant difference between treatment groups in number of adverse events was observed. Higher rate of edema was reported with pioglitazone (5.9 vs 2.5%).</p> <p>Weight loss was observed with placebo (-1.36 kg) while patients receiving pioglitazone had weight gain (0.95 kg; P value not reported).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Kaku et al.¹⁰⁴ (2009)</p> <p>Metformin 500 to 750 mg daily</p> <p>vs</p> <p>pioglitazone 15 to 30 mg QD and metformin 500 to 750 mg daily</p>	<p>DB, PC, PG, RCT</p> <p>Patients 20 to 65 years of age with type 2 diabetes, HbA_{1c} 6.5 to 10.0%, who were drug naïve or on metformin monotherapy</p>	<p>N=169</p> <p>28 weeks</p>	<p>Primary: HbA_{1c}, FPG, fasting insulin, insulin resistance, lipid parameters</p> <p>Secondary: Not reported</p>	<p>Primary: At week 28, mean change in HbA_{1c} from baseline was -0.67% with pioglitazone compared to 0.25% with placebo (P<0.0001).</p> <p>More patients receiving pioglitazone achieved an HbA_{1c} <6.5% compared to placebo (38.6 vs 8.1%, respectively; P<0.0001).</p> <p>At week 28, mean change in FPG from baseline was -20.5 mg/dL with pioglitazone compared to 1.9 mg/dL with placebo (P<0.0001).</p> <p>Mean fasting insulin concentrations were reduced to a greater extent with pioglitazone (-2.15 mU/mL) compared to placebo (-0.38 mU/mL; P=0.021).</p> <p>Insulin resistance was reduced more by pioglitazone compared to placebo (-1.34 vs -0.15; P=0.0025).</p> <p>The main differences in lipids between pioglitazone compared to placebo were significant increases in TC (P=0.0057) and HDL-C (P<0.0001). Adiponectin levels were significantly increased by pioglitazone compared to placebo (P=0.0001).</p> <p>Secondary: Not reported</p>
<p>Perez et al.¹⁰⁵ (2009)</p> <p>Pioglitazone/metformin 15/850 mg BID</p> <p>vs</p> <p>pioglitazone 15 mg BID</p> <p>vs</p>	<p>DB, PG, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes, HbA_{1c} 7.5 to 10.0%, BMI ≤45 kg/m², who were drug naïve</p>	<p>N=600</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: HbA_{1c} responder rate, changes in baseline FPG, fasting insulin, insulin resistance</p>	<p>Primary: At week 24, mean change in HbA_{1c} from baseline was -1.83% with pioglitazone/metformin compared to -0.96% pioglitazone and -0.99% with metformin (P<0.0001 for combination therapy vs either monotherapy).</p> <p>Secondary: In the pioglitazone/metformin group, 63.8% achieved HbA_{1c} <7.0% compared to 46.9% with pioglitazone and 38.9% with metformin (P value not reported).</p> <p>Pioglitazone/metformin led to the greatest reduction in FPG from baseline to final visit (-39.9 mg/dL) compared to -22.2 mg/dL with pioglitazone and -24.8 mg/dL with metformin (P<0.01 for combination therapy vs</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 850 mg BID				<p>either monotherapy).</p> <p>Pioglitazone/metformin led to the greatest reduction in fasting insulin from baseline to final visit (-3.91 μIU/mL), followed by pioglitazone (-3.18 μIU/mL). Both reductions were significantly greater compared to metformin (-0.98 μIU/mL; P<0.05).</p> <p>At week 24, the greatest decrease in insulin resistance was seen with pioglitazone/metformin and pioglitazone compared to metformin; however, the difference was significant only with pioglitazone/metformin (P<0.01).</p>
<p>Seufert et al.¹⁰⁶ (2008)</p> <p><u>Study 1</u> Metformin (existing therapy) and pioglitazone 15 to 45 mg QD</p> <p>vs</p> <p>metformin (existing therapy) and gliclazide† 80 to 320 mg daily</p> <p><u>Study 2</u> Metformin 850 to 2,550 mg daily and sulfonylurea</p> <p>vs</p> <p>pioglitazone 15 to 45 mg QD and sulfonylurea</p>	<p>2 MC, RCT</p> <p>Patients 35 to 75 years of age with type 2 diabetes who were inadequately controlled on either metformin or sulfonylurea monotherapy (HbA_{1c} 7.5 to 11.0%), and fasting C-peptide >1.5 ng/mL)</p>	<p>N=1,269</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline, FPG, glucose excursions using Three hour oral glucose tolerance test, insulin sensitivity</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Study 1</i> The mean change in HbA_{1c} from baseline to week 104 was -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20).</p> <p>The mean change in FPG from baseline to week 104 was -1.8 mmol/L with pioglitazone and metformin compared to -1.1 mmol/L with gliclazide and metformin (P<0.001).</p> <p>Pioglitazone therapy in patients failing metformin therapy achieved decreases in glucose excursions at the end of the two-year treatment period. This effect was not seen in the patients receiving gliclazide for two years as add-on therapy to failing metformin.</p> <p>Insulin sensitivity increased when pioglitazone was added to metformin therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001).</p> <p><i>Study 2</i> The mean change in HbA_{1c} from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173).</p> <p>The mean change in FPG from baseline to week 104 was -2.0 mmol/l with pioglitazone and sulfonylurea compared to -1.9 mmol/l with metformin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy (existing therapy)				and sulfonylurea (P=0.506). The addition of pioglitazone to failing sulfonylurea therapy for two years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment. Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to sulfonylurea (P=0.581 between treatments). Secondary: Not reported
Matthews et al. ¹⁰⁷ (2005) Metformin (existing therapy) and pioglitazone 15 to 45 mg QD vs metformin (existing therapy) and gliclazide† 80 to 320 mg QD	DB, RCT Patients with type 2 diabetes that was poorly controlled (HbA _{1c} 7.5 to 11.0%) with metformin monotherapy	N=630 12 months	Primary: Effect on HbA _{1c} Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in HbA _{1c} were observed in pioglitazone- (-0.99%) and gliclazide-treated groups (-1.01%; P=0.837). Secondary: Similar reductions in FPG were observed in pioglitazone- (-2.1 mmol/L) and gliclazide- (-1.6 mmol/L) treated groups (P=0.506). Gliclazide significantly reduced LDL-C compared to pioglitazone (-4.2 mg/dL vs +10.4 mg/dL; P=0.001). Pioglitazone significantly reduced TG (-53.1 vs -19.5 mg/dL; P<0.001) and increased HDL-C (6.9 mg/dL vs no change; P<0.001) compared to gliclazide.
Charbonnel et al. ¹⁰⁸ (2005) Metformin (existing therapy) and pioglitazone 15 to 45 mg QD vs metformin	DB, RCT Patients with type 2 diabetes that was poorly controlled (HbA _{1c} 7.5 to 11.0%) with metformin monotherapy	N=630 24 months	Primary: Effect on HbA _{1c} Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in HbA _{1c} were observed with pioglitazone add-on therapy (-0.89%) and with gliclazide add-on therapy (-0.77%; P=0.200) after two years. Secondary: Significant reductions in FPG were observed with pioglitazone add-on therapy (-1.8 mmol/L) compared to gliclazide add-on therapy (-1.1 mmol/L; P<0.001) after two years. Gliclazide add-on therapy had significantly reduced LDL-C compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(existing therapy) and gliclazide† 80 to 320 mg QD				<p>pioglitazone add-on therapy (-6 vs +2 mg/dL; P<0.001).</p> <p>Pioglitazone add-on therapy significantly reduced TG (-23 vs -7 mg/dL; P<0.001) and increased HDL-C (22 vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy.</p> <p>No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported.</p> <p>Less weight gain was observed with gliclazide add-on therapy to metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg).</p>
<p>Hanefeld et al.¹⁰⁹ (2004)</p> <p>Metformin 850 to 2,250 mg daily and sulfonylurea (existing therapy)</p> <p>vs</p> <p>pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy)</p>	<p>DB, MC, PG, RCT</p> <p>Patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy</p>	<p>N=639</p> <p>12 months</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: FPG, fasting plasma insulin, lipids, urinary albumin and creatinine (to determine albumin-to-creatinine ratio)</p>	<p>Primary: HbA_{1c} was reduced by 1.20 and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments).</p> <p>Secondary: FPG (P=0.528) and fasting plasma insulin (P=0.199) were also reduced but the between-treatment differences were not statistically significant.</p> <p>Pioglitazone addition to sulfonylurea significantly reduced TG (-16 vs -9%; P=0.008) and increased HDL-C (14 vs 8%; P<0.001) compared with metformin addition.</p> <p>LDL-C was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001).</p> <p>Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone group and increased 2% in the metformin group (P=0.017).</p> <p>Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group.</p>
<p>Comaschi et al.¹¹⁰ (2008)</p> <p>Metformin/glibenclamide* 400/2.5 mg</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥35 years of age with type 2 diabetes who had received treatment</p>	<p>N=250</p> <p>6 months</p>	<p>Primary: Change in HbA_{1c} from baseline to six months</p> <p>Secondary:</p>	<p>Primary: Pioglitazone-based combination therapy and fixed-dose metformin/glibenclamide resulted in similar reductions in HbA_{1c} (-1.11 vs -1.29%, respectively; P=0.192) and FPG (-2.13 vs -1.81 mmol/L, respectively; P=0.370).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>1 to 3 tablets daily vs pioglitazone 15 to 30 mg QD as add-on to existing oral hypoglycemic therapy (either metformin or sulfonylurea)</p>	<p>with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months before study entry, HbA_{1c} 7.5 to 11.0%, and fasting C-peptide >0.33 nmol/L</p>		<p>Change in lipid profiles after six months of treatment</p>	<p>Secondary: No changes in TC were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479).</p> <p>The addition of pioglitazone to metformin or a sulfonylurea led to a slight increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001).</p> <p>There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.01 mmol/L; P=0.677).</p> <p>There was no significant change in LDL-C in patients treated with pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425)</p> <p>There was a significant reduction in TGs with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045).</p>
<p>Abdul-Ghani et al.¹¹¹ (2015) EDICT Metformin (escalating dose) vs triple therapy (metformin/pioglitazone/exenatide)</p>	<p>OL, RCT Drug-naïve, recently diagnosed (<2 years) subjects 30 to 75 years of age with type 2 diabetes mellitus</p>	<p>N=221 2 years</p>	<p>Primary: HbA_{1c} Secondary: Percentage of participants achieving HbA_{1c} <6.5 and <7.0%; decrease in fasting and postprandial plasma glucose; change in body weight; and rate of hypoglycemic events</p>	<p>Primary: Baseline HbA_{1c} was identical in both groups (8.6%) and during the first six months decreased in both treatment arms. At six months, there was a small but significant HbA_{1c} difference (0.2%, P=0.03) between groups (triple therapy 6.0% vs metformin therapy 6.2%). After six months, HbA_{1c} gradually increased with metformin therapy to 6.5% at 24 months and remained stable at 5.95% with triple therapy; thus, the difference in HbA_{1c} between the two treatments progressively increased with time and was significantly different at two years (change in HbA_{1c} 0.55%; P<0.0001).</p> <p>Secondary: More participants receiving metformin therapy failed to maintain the treatment goal (HbA_{1c} <6.5%) than did those receiving triple therapy (44 vs 17%; P=0.003). A total of 40 participants receiving metformin therapy failed to maintain HbA_{1c} at <6.5% at/after six months compared with only 13 participants receiving triple therapy (P<0.0001). More participants receiving triple therapy (61%) had HbA_{1c} reduced to the normal range</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>(<6.0%) than those receiving metformin therapy (27%; P<0.0001). The median HbA_{1c} of participants receiving triple therapy was 5.9% compared with 6.4% for those receiving metformin therapy. More than 90% of participants receiving triple therapy maintained HbA_{1c} at <7.0% versus <75% of participants receiving metformin therapy.</p> <p>The most common adverse event was hypoglycemia, reported by 46 and 14% of participants receiving metformin and triple therapy, respectively. The overall frequency of hypoglycemic events was greater in participants receiving metformin therapy (2.2 vs 0.31 events/participant per year; P<0.0001).</p>
<p>Borges et al.¹¹² (2011)</p> <p>Rosiglitazone/metformin</p> <p>vs</p> <p>metformin</p>	<p>DB, MC, RCT</p> <p>Drug naïve patients with type 2 diabetes</p>	<p>N=688</p> <p>18 months</p>	<p>Primary: Change in baseline HbA_{1c}, FPG</p> <p>Secondary: Bone mineral density</p>	<p>Primary: Combination therapy was more efficacious in achieving significant reductions in HbA_{1c} (P<0.0001) and FPG (P<0.001) compared to metformin. In addition, more patients achieved HbA_{1c} and FPG goals with combination therapy compared to metformin.</p> <p>Secondary: In a bone substudy, at week 80 combination therapy was associated with significantly lower bone mineral density compared to metformin in the lumbar spine (P<0.0012) and total hip (P=0.0005, respectively). There was no difference between treatments for distal one-third of radius, femoral neck, and total bone mineral densities (P values not reported).</p>
<p>Fonseca et al.¹¹³ (2000)</p> <p>Metformin 2,500 mg daily</p> <p>vs</p> <p>metformin 2,500 mg and rosiglitazone 4 mg daily</p> <p>vs</p>	<p>DB, PC, RCT</p> <p>Patients with poorly controlled type 2 diabetes (mean FPG 140 to 300 mg/dL) with metformin; baseline HbA_{1c} 8.6% in the metformin treatment group, 8.9% in the rosiglitazone/metformin 4/2,500</p>	<p>N=348</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, fructosamine, C-peptide, FFA, lipids, lactate, and estimates of insulin sensitivity (HOMA-S) and β-cell function (HOMA-B)</p> <p>Secondary: Not reported</p>	<p>Primary: Addition of rosiglitazone significantly reduced HbA_{1c} in a dose-related fashion from baseline compared to metformin monotherapy. Mean difference from the metformin control group was -1.0% (P<0.001) with rosiglitazone/metformin 4/2,500 mg and -1.2% with rosiglitazone/metformin 8/2,500 mg (P<0.001).</p> <p>Mean FPG concentrations were reduced significantly with rosiglitazone/metformin 4/2,500 mg (-33 mg/dL; P<0.0001) and with rosiglitazone/metformin 8/2,500 mg (-48.4 mg/dL; P<0.0001). No significant change in FPG was observed with metformin monotherapy.</p> <p>Fructosamine levels were reduced with both rosiglitazone/metformin 4/2,500 mg (-27.9 μmol/L; P value not reported) and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 2,500 mg and rosiglitazone 8 mg daily	mg treatment group and 8.9% in the rosiglitazone/metformin 8/2,500 mg treatment group; patients were excluded if they had NYHA class III-IV heart failure, angina, renal or liver disease, symptomatic neuropathy, or prior use of rosiglitazone or insulin			<p>rosiglitazone/metformin 8/2,500 mg (-36.8 $\mu\text{mol/L}$; P value not reported). Fructosamine levels increased with metformin monotherapy (12.3 $\mu\text{mol/L}$; P value not reported).</p> <p>C-peptide values were reduced significantly in all treatment groups compared to baseline (P<0.05).</p> <p>FFA levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05).</p> <p>Significant increases in TC, HDL-C and LDL-C were observed with both rosiglitazone groups when compared to metformin monotherapy group (P<0.05).</p> <p>Mean fasting lactate levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05).</p> <p>Both insulin sensitivity (as measured by HOMA-S) and β-cell function (as measured by HOMA-B) were increased in a dose-dependent fashion with rosiglitazone/metformin compared to metformin monotherapy (P value not reported).</p> <p>Secondary: Not reported</p>
Weissman et al. ¹¹⁴ (2005) Metformin 1,500 mg QD (MET) vs rosiglitazone 8 mg QD and metformin 1,000 mg QD (RSG + MET)	DB, MC, PG, RCT Patients 18 to 75 years of age diagnosed with type 2 diabetes (defined as HbA _{1c} 6.5 to 8.5% for patients receiving combination therapy with metformin and	N=766 2-week wash out period followed by 4 to 7 weeks of run-in period and 24 weeks of treatment	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG at week 24, proportion of patients responding to treatment (reduction $\geq 0.7\%$ for HbA _{1c} and ≥ 30	Primary: After 24 weeks, RSG+MET and MET were both effective in improving HbA _{1c} with mean reductions of -0.93% (95% CI, -1.06 to -0.80) and -0.71% (95% CI, -0.83 to -0.60), respectively, with a mean treatment difference of -0.20% (95% CI, -0.36 to -0.04). Secondary: Significant reductions in FPG from baseline were seen in patients receiving RSG+MET (-2.29 mmol/L; 95% CI, -2.59 to -1.99) compared to patients receiving MET (-1.12 mmol/L; 95% CI, -1.43 to -0.82), with a treatment difference of -0.85 mmol/L (95% CI, -1.23 to -0.47).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>sulfonylurea or HbA_{1c} 7.0 to 10.0% for drug-naïve or patients receiving monotherapy), FPG of 126 to 270 mg/dL and BMI ≥27kg/m²; any subjects previously receiving metformin or metformin and sulfonylurea must have received ≤metformin 1,000 mg/day for at least 3 months prior to study entry and patients must have stopped previous treatment with TZD at least 3 months prior to screening</p>		<p>mg/dL for FPG at week 24), clinical safety, adverse events, tolerability, clinical laboratory tests</p>	<p>The proportion of patients who responded to treatment (reduction in HbA_{1c} ≥0.7%) was greater in the RSG+MET group than the MET group (59.5 and 49.5%, respectively) with the treatment difference of 10% (95% CI, 1.9 to 18.1).</p> <p>The proportion of FPG responders (reduction in FPG ≥30 mg/dL) was also greater in the RSG+MET group than in the MET group (55.0 vs 32.5%, respectively).</p> <p>The percentage of patients experiencing a gastrointestinal effect was greater in the MET group compared to the RSG+MET group (38.7 and 27.9%). The odds of experiencing a gastrointestinal side effect were 63% greater for patients receiving MET compared to patients receiving RSG+MET (OR, 1.63; 95% CI, 1.19 to 2.24).</p> <p>RSG+MET resulted in a mean weight gain of 1.79 kg (P<0.0001) compared to a mean weight loss of -1.78 kg (P<0.001) with MET.</p> <p>There were three deaths during the course of the study with two prior to DB study medication, and one while on RSG+MET; the cause of which was unknown, although it was not considered to be treatment related.</p>
<p>Stewart et al.¹¹⁵ (2006)</p> <p>Metformin 3,000 mg/day (MET)</p> <p>vs</p> <p>metformin 2,000 mg daily and rosiglitazone 8 mg daily (MET + RSG)</p>	<p>DB, MC, PG, RCT</p> <p>Type 2 diabetic patients 18 to 70 years of age, who were either antidiabetic-drug-naïve with FPG of 7.0 to 9.0 mmol/L and HbA_{1c} 7.0 to 9.0%, or previously treated with oral antidiabetic monotherapy with</p>	<p>N=526</p> <p>32 weeks</p>	<p>Primary: Proportion of patients achieving HbA_{1c} ≤6.5% at week 32, change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving target HbA_{1c} and FPG levels, change in baseline FPG and fasting plasma</p>	<p>Primary: At week 32, there was a reduction from baseline in mean HbA_{1c} in the MET+RSG group from 7.2 to 6.7% compared to 7.2 to 6.8% in the MET group (P=0.0357).</p> <p>Secondary: The proportion of patients achieving HbA_{1c} ≤6.5% at week 32 was similar in the two groups (P=0.095).</p> <p>The proportion of patients achieving FPG <7.0 mmol/L at week 32 was 56% in the MET+RSG group compared to 38% in the MET group (OR, 2.33; P<0.0001).</p> <p>The reduction in fasting plasma insulin from baseline was greater in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	FPG 6.0 to 8.0 mmol/L and HbA _{1c} 6.5 to 8.0%		insulin, change in insulin resistance, pancreatic β -cell function, CRP, lipid parameters and 24-hour ambulatory BP, safety	<p>MET+RSG group compared to the MET group (treatment difference, -12.2 pmol/L; P=0.00029).</p> <p>Homeostasis model assessment estimated that insulin sensitivity, β-cell function, CRP, and SBP were greater in the MET+RSG group at week 32 compared to the MET group (P<0.05 for all).</p> <p>TC, HDL-C, and LDL-C increased, free fatty acids decreased, and TG did not change in the MET+RSG group, whereas in the MET group there were decreases in TC, LDL-C, and TG, and increases in HDL-C and FFA. The difference between the treatments was significant for the above parameters (P<0.05).</p> <p>The proportion of patients with reductions in 24-hour mean SBP was greater in the MET+RSG group compared to the MET group (treatment difference, -3.6 mm Hg; P=0.0315).</p> <p>The overall incidences of gastrointestinal adverse events were comparable between groups, but there was a lower incidence of diarrhea in the MET+RSG group (8 vs 18%). Hypoglycemia was reported in 17 patients (7%) in the MET+RSG group compared to 10 patients (4%) in the MET group.</p> <p>There were greater reductions in mean hemoglobin and hematocrit over 32 weeks in the MET+RSG group compared to the MET group (P<0.0001).</p>
Rosak et al. ¹¹⁶ (2005) Metformin (existing therapy) and rosiglitazone 4 to 8 mg	OS, PM Two studies in which type 2 diabetics on metformin therapy received rosiglitazone add-on therapy; baseline HbA _{1c} was 8.1% in both trials	N=11,014 6 months	Primary: Change in baseline HbA _{1c} , FPG, body weight, and BP Secondary: Not reported	<p>Primary: Addition of rosiglitazone significantly reduced HbA_{1c} from baseline (-1.3%; P<0.0001).</p> <p>Addition of rosiglitazone significantly reduced FPG from baseline (-47.0 mg/dL; P<0.0001).</p> <p>Significant reduction in BP from baseline (-7/-3 mm Hg; P<0.0001) was observed with rosiglitazone add-on therapy.</p> <p>Significant reduction in weight (-1.7 kg; P<0.0001) was observed with rosiglitazone add-on therapy.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Most commonly reported adverse events were weight gain (0.16%) and edema (0.15%).</p> <p>Secondary: Not reported</p>
<p>Bailey et al.¹¹⁷ (2005)</p> <p>Metformin 2,500 to 3,000 mg daily</p> <p>vs</p> <p>rosiglitazone/ metformin 4/1,000 to 8/2,000 mg daily</p>	<p>DB, MC, PG, RCT</p> <p>Patients with type 2 diabetes poorly controlled (FPG ≥ 126 to 216 mg/dL) with metformin alone or in combination with an insulin secretagogue or acarbose; baseline HbA_{1c} 7.4% for rosiglitazone add-on therapy and 7.5% for metformin; patients were excluded if they had been treated with a TZD or insulin, had unstable cardiovascular or cerebrovascular conditions, or had uncontrolled hypertension</p>	<p>N=568</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and insulin, proportion of patients who achieved HbA_{1c} and FPG targets</p>	<p>Primary: Reductions in HbA_{1c} observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-0.22% difference between treatment groups; P=0.001).</p> <p>Secondary: Reductions in FPG observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-18.3 mg/dL difference between treatment groups; P<0.001).</p> <p>Significant reduction in fasting insulin was observed with rosiglitazone add-on therapy compared to metformin monotherapy (-12.4 pmol/L difference between treatment groups; P=0.001).</p> <p>Greater proportion of patients on rosiglitazone add-on therapy (54%) reached HbA_{1c} targets (<7.0%) compared to those treated with metformin monotherapy (36%; OR, 2.42; P<0.001).</p> <p>Greater proportion of patients on rosiglitazone add-on therapy (32%) reached FPG targets (<126 mg/dL) compared to those treated with metformin monotherapy (8%; OR, 5.71; P<0.001).</p> <p>Higher rate of withdrawal due to adverse events with metformin monotherapy (8 vs 4%; no P value reported) was noted. Gastrointestinal disorders were the most commonly reported event that caused withdrawal in the metformin monotherapy group.</p>
<p>Rosenstock et al.¹¹⁸ (2006)</p> <p>Metformin 500 to</p>	<p>DB, MC, RCT</p> <p>Type 2 diabetics with HbA_{1c} >7.5 to</p>	<p>N=468</p> <p>32 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p>	<p>Primary: Patients receiving rosiglitazone/metformin showed significant improvements in HbA_{1c} with a reduction of -2.3% compared to baseline vs -1.8% with patients receiving metformin (P<0.0008) and -1.6% with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>2,000 mg daily</p> <p>vs</p> <p>rosiglitazone 4 to 8 mg daily</p> <p>vs</p> <p>rosiglitazone/ metformin 4/1,000 to 8/2,000 mg daily</p>	<p>11.0%, with FPG \leq270 mg/dL who were previously treated with diet and exercise or had not been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening</p>		<p>Secondary: Proportion of patients achieving HbA_{1c} and FPG targets, change in baseline FPG, safety</p>	<p>patients receiving rosiglitazone (P<0.0001).</p> <p>Secondary: Target HbA_{1c} \leq6.5 and <7.0% were achieved in more patients in the rosiglitazone/metformin group (60 and 77%) than in the metformin (39 and 57%) or rosiglitazone (35 and 58%) groups, respectively (P values not reported).</p> <p>The greatest mean decrease in FPG was seen with rosiglitazone/metformin (-74 mg/dL) and was significant compared to metformin (-50 mg/dL; P<0.0001) and rosiglitazone (-47 mg/dL; P<0.0001).</p> <p>Treatment was well tolerated with nausea, vomiting and diarrhea as the most commonly reported adverse events. Edema was comparable between rosiglitazone/metformin (6%) and rosiglitazone (7%) and lower with metformin.</p>
<p>TODAY Study Group.¹¹⁹ (2012)</p> <p>TODAY</p> <p>Metformin</p> <p>vs</p> <p>rosiglitazone 4 mg BID plus metformin</p> <p>vs</p> <p>metformin plus lifestyle intervention (focusing on weight loss through eating and</p>	<p>MC, RCT</p> <p>Patients 10 to 17 years of age, with type 2 diabetes</p>	<p>N=699</p> <p>3.86 years (average follow-up)</p>	<p>Primary: Loss of glycemic control (HbA_{1c} \geq8.0% for six months or sustained metabolic decompensation requiring insulin)</p> <p>Secondary: Body weight, metabolic outcomes, safety</p>	<p>Primary: Overall, a total of 319 (45.6%) patients reached the primary outcome, with a median time to treatment failure of 11.5 months (range, <1 to 66). Rates of failure were 51.7 (95% CI, 45.3 to 58.2), 38.6 (95% CI, 32.4 to 44.9), and 46.6% (95% CI, 40.2 to 53.0) of patients on metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention, respectively.</p> <p>Rosiglitazone plus metformin was more efficacious to metformin; combination therapy was associated with a 25.3% decrease in the occurrence of the primary outcome compared to metformin (P=0.006). The outcome with metformin plus lifestyle intervention was intermediate, but not significantly different from metformin or rosiglitazone plus metformin (P value not reported). The reasons for treatment failure did not differ significantly across treatments.</p> <p>Prespecified analyses according to sex and race or ethnic group showed differences in sustained effectiveness, with metformin least effective in non-Hispanic black patients and rosiglitazone plus metformin most effective in female patients.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>activity behaviors)</p> <p>Patients were treated during a run-in period of 2 to 6 months with metformin 1,000 mg BID to attain an HbA_{1c} <8.0% prior to randomization.</p>				<p>BMI over time (up to 60 months) differed significantly according to the study treatment (P<0.001 for the overall comparison), and the results of all three pairwise comparisons between treatment groups were also significant. Patients treated with rosiglitazone plus metformin had the greatest increase in BMI and patients receiving metformin plus lifestyle intervention had the least.</p> <p>The change in fat mass from baseline differed significantly across the treatment groups (P<0.05) because of a significant difference between rosiglitazone plus metformin and metformin plus lifestyle interventions. There were no significant between-group differences in the change from baseline for any other outcome.</p> <p>Serious adverse events were reported in 19.2% of all patients, including 18.1, 14.6, and 24.8% with metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention (P=0.02). Hospitalizations accounted for more than 90% of serious adverse events. Severe hypoglycemia occurred in one, one, and two patients receiving metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention. No effects of rosiglitazone on bone mineral content or rate of fracture were noted.</p>
<p>Home et al.¹²⁰ (2007) RECORD Interim Analysis</p> <p>Metformin plus a sulfonylurea</p> <p>vs</p> <p>rosiglitazone plus either metformin or a sulfonylurea</p>	<p>MC, OL, RCT</p> <p>Patients with type 2 diabetes between the ages of 40 and 75 years, BMI >25.0 kg/m², HbA_{1c} 7.1 to 9.0% while receiving maximum permitted or tolerated doses of metformin or a sulfonylurea; exclusion criteria were the current use of other glucose-lowering agents,</p>	<p>N=4,447 (n=1,117 rosiglitazone plus metformin; n=1,103 rosiglitazone plus sulfonylurea; n=2,227 metformin plus sulfonylurea)</p> <p>Mean follow-up 3.75 years for the</p>	<p>Primary: Hospitalization or death from cardiovascular causes</p> <p>Secondary: Death from cardiovascular causes and from any cause, MI, congestive heart failure, and composite of death from cardiovascular causes, MI and</p>	<p>Primary: For adjudicated primary end points (hospitalization or death from cardiovascular causes), the HR was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication.</p> <p>Secondary: There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension	unplanned interim analyses (study was designed to be 6 years)	stroke	Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006).
Home et al. ¹²¹ (2009) RECORD Metformin plus a sulfonylurea vs rosiglitazone plus either metformin or a sulfonylurea	MC, OL, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI ≥ 25 kg/m ² , on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA _{1c} 7.0 to 9.0%)	N=4,458 5.5 years (mean follow-up)	Primary: Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke	Primary: The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 patients receiving rosiglitazone and active control, respectively (HR, 0.99; 95% CI, 0.85 to 1.16; P=0.93). Secondary: There was no significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR, 0.84; 95% CI, 0.59 to 1.18; P=0.32), all-cause mortality (HR, 0.86; 95% CI, 0.68 to 1.08; P=0.19), MI (HR, 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR, 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of cardiovascular death, MI, or stroke (HR, 0.93; 95% CI, 0.74 to 1.15; P=0.50). Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR, 2.10; 95% CI, 1.35 to 3.27; P=0.0010). There were no serious adverse event reports of macular edema. The incidence of bone fractures was higher with rosiglitazone compared to active control (RR, 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR, 1.82; 95% CI, 1.37 to 2.41 vs RR, 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rosiglitazone was primarily in the upper limb (RR, 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR, 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures.
Mahaffey et al. ¹²² (2013) RECORD re-evaluation Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	RETRO Patients 40 to 75 years of age with type 2 diabetes and BMI \geq 25 kg/m ² , on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA _{1c} 7.0 to 9.0%)	N=4,458 5.5 years (mean follow-up)	Primary: Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke	Primary: For the primary end point (time to first occurrence of CV (or unknown cause) death, MI, or stroke) no statistically significant difference was observed between rosiglitazone and metformin/sulfonylurea using the original RECORD end point definitions (HR, 0.95; 95% CI, 0.78 to 1.17). For the primary end point, no meaningful difference between rosiglitazone and metformin/sulfonylurea was observed using the original RECORD end point definitions (HR, 0.95; 95% CI 0.78 to 1.17) or new FDA end point definitions (HR, 0.97; 95% CI, 0.79 to 1.18). Furthermore, these results are similar to results from the original RECORD study (HR, 0.93; 95% CI, 0.74 to 1.15). Secondary: The original RECORD study results and the Duke Clinical Research Institute clinical events classification results were also similar for the individual components of the composite end point. These findings and the additional sensitivity analyses performed support the original RECORD results and suggest that when using essentially the same data, the observations were not affected by different clinical events classification processes, physician adjudicators, or end point definitions.
Home et al. ¹²³ (2007) Metformin plus a sulfonylurea vs rosiglitazone plus either metformin or a sulfonylurea	MC, OL, PG, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI \geq 25 kg/m ² , on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control	N=1,122 18 months	Primary: Change in baseline HbA _{1c} Secondary: FPG, serum lipids, HOMA basal insulin sensitivity and islet β -cell function (HOMA % β), body weight, inflammatory/	Primary: At 18 months, HbA _{1c} reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference, 0.07%; 95% CI, -0.09 to 0.23; P value not significant), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference, 0.06%; 95% CI, -0.09 to 0.20; P value not significant). Secondary: Differences in FPG were not significant at 18 months (rosiglitazone vs sulfonylurea, -0.36 mmol/L; P=0.062 and rosiglitazone vs metformin, -0.34 mmol/L; P=0.089).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	(HbA _{1c} 7.0 to 9.0%)		thrombotic markers, CRP	<p>Rosiglitazone increased TC (P≤0.001) and LDL-C (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared to the control. An increase in HDL-C and TG was observed with rosiglitazone compared to sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001, 0.40 vs 0.15 mmol/L; P=0.016, respectively), but not with metformin (P value not significant for both).</p> <p>HOMA-estimated basal insulin sensitivity was substantially increased with rosiglitazone compared to the respective controls (P<0.001 for both). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, to a similar extent (P value not significant).</p> <p>Rosiglitazone was associated with a significant increase in body weight compared to metformin (P<0.001) and a sulfonylurea (P=0.003).</p> <p>At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to sulfonylureas (-5.7 vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P value not significant).</p> <p>There was a significant reduction in CRP with rosiglitazone compared to a sulfonylurea (P<0.001) and metformin (P=0.001).</p>
<p>Komajda et al.¹²⁴ (2008) RECORD</p> <p>Metformin plus a sulfonylurea</p> <p>vs</p> <p>rosiglitazone plus either metformin or a sulfonylurea</p>	<p>MC, OL, RCT</p> <p>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m², on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)</p>	<p>N=668</p> <p>12 months</p>	<p>Primary: Change from baseline in 24-hour ambulatory BP at six months and 12 months</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>For patients receiving rosiglitazone and a sulfonylurea, the reduction in 24-hour SBP was greater at six months (-3.8 mm Hg) and 12 months (-3.8 mm Hg) than with metformin and sulfonylurea therapy (-1.2 mm Hg and -1.3 mm Hg, respectively; six months, P=0.015; 12 months, P=0.031).</p> <p>Reductions in 24-hour DBP were greater at 6 months and 12 months for patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mm Hg) compared to metformin and sulfonylurea (-0.4 mm Hg and -0.6 mm Hg; both P<0.001).</p> <p>At 12 months, the reduction in 24-hour SBP was greater for rosiglitazone and metformin (-4.9 mm Hg) than for metformin and sulfonylurea (-2.2</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>mm Hg; P=0.016).</p> <p>At 12 months, the reduction in DBP was greater for rosiglitazone and metformin (-3.8 mmHg) than for metformin and sulfonylurea (-1.7 mm Hg; P=0.003).</p> <p>At six months, the reductions in SBP and DBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (SBP; P value not significant, DBP; P=0.049).</p> <p>Secondary: Not reported</p>
<p>Hamann et al.¹²⁵ (2008)</p> <p>Metformin 2,000 mg daily and glibenclamide* 5 mg or gliclazide† 80 mg (SU+MET)</p> <p>vs</p> <p>rosiglitazone/ metformin fixed dose combination 4/2,000 mg daily (RSG+MET)</p>	<p>DB, PG, RCT</p> <p>Overweight patients (BMI ≥25 kg/m²) with type 2 diabetes, HbA_{1c} 7.0 to 10.0%, who received metformin ≥850 mg/day for at least 8 weeks</p>	<p>N=596</p> <p>52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 52</p> <p>Secondary: Change in FPG, β-cell function, insulin resistance, hypoglycemia, BP</p>	<p>Primary: At week 52, mean change in HbA_{1c} from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25).</p> <p>Secondary: Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095).</p> <p>The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs 0.055 HbA_{1c}%/year, respectively; P=0.0002).</p> <p>Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001).</p> <p>Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001).</p> <p>After 52 weeks, 24-hour diastolic and systolic ambulatory BPs were reduced with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ambulatory BPs (-2.9 mm Hg; P=0.0013), but not for systolic ambulatory BP (-2.6 mm Hg; P=0.0549).</p>
Diabetes Prevention Studies				
<p>Knowler et al.¹²⁶ (2002)</p>	<p>DB, MC, PC, RCT</p>	<p>N=3,234</p>	<p>Primary: Diabetes,</p>	<p>Primary: Incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Metformin 850 mg BID</p> <p>vs</p> <p>placebo with standard lifestyle recommendations</p> <p>vs</p> <p>intensive lifestyle modifications designed to achieve and maintain both a 7% weight loss and 150 minutes of exercise a week</p>	<p>Nondiabetic patients ≥ 25 years of age at high risk with elevated fasting and post-load plasma glucose concentrations, BMI ≥ 24 kg/m² or ≥ 22 kg/m² for Asian patients, a plasma glucose concentration 95 to 125 mg/dL, and 140 to 199 mg/dL 2 hours after a 75 g oral glucose load</p>	<p>2.8 years (mean)</p>	<p>diagnosed on the basis of an annual oral glucose-tolerance test or a semiannual FPG test, according to the 1997 criteria of the American Diabetes Association: a value for plasma glucose of 126 mg/dL or higher in the fasting state or 200 mg/dL or higher two hours after a 75 g oral glucose load</p> <p>Secondary: Not reported</p>	<p>the placebo, metformin, and intensive lifestyle-intervention groups, respectively.</p> <p>Incidence of diabetes was 58% lower (95% CI, 48 to 66) in the intensive lifestyle-intervention group and 31% lower (95% CI, 17 to 43) in the metformin group than in the placebo group.</p> <p>Incidence of diabetes was 39% lower (95% CI, 24 to 51) in the intensive lifestyle-intervention group than in the metformin group.</p> <p>Incidence of diabetes differed significantly among the three groups (P<0.001 for each comparison).</p> <p>The estimated cumulative incidence of diabetes at three years was 28.9, 21.7, and 14.4% in the placebo, metformin, and intensive lifestyle groups, respectively. Using these results, to prevent one case of diabetes during a three-year period, 6.9 persons would have to participate in the intensive lifestyle-intervention group and 13.9 persons would have to receive metformin.</p> <p>Secondary: Not reported</p>
<p>Orchard et al.¹²⁷ (2005)</p> <p>Metformin 850 mg BID</p> <p>vs</p> <p>placebo with standard lifestyle recommendations</p> <p>vs</p> <p>intensive lifestyle</p>	<p>DB, MC, PC, RCT</p> <p>Nondiabetic patients ≥ 25 years of age at high risk with elevated fasting and post-load plasma glucose concentrations, BMI ≥ 24 kg/m² or ≥ 22 kg/m² for Asian patients, a plasma glucose concentration 95 to 125 mg/dL, and 140</p>	<p>N=3,234</p> <p>3.2 years (mean)</p>	<p>Primary: Prevalence of the metabolic syndrome at baseline in the Diabetes Prevention Program and the incidence of new cases after intensive lifestyle intervention and metformin</p> <p>Secondary:</p>	<p>Primary: Fifty-three percent of the patients fulfilled the criteria for the metabolic syndrome; this proportion was relatively constant by age.</p> <p>Incidence of the metabolic syndrome was reduced by 41% in the intensive lifestyle group (P<0.001) and by 17% in the metformin group (P=0.03) compared to the placebo group.</p> <p>Resolution of metabolic syndrome in participants who had the syndrome at baseline was significant for intensive lifestyle interventions vs placebo (P=0.002). The prevalence at three years varied significantly by treatment group (P<0.001): 18% of the placebo group, 23% of the metformin group, and 38% of the intensive lifestyle group no longer had the syndrome.</p> <p>Prevalence of the metabolic syndrome in all participants increased from</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
modifications designed to achieve and maintain a 7% weight loss and 150 minutes of exercise a week	to 199 mg/dL two hours after a 75 gram oral glucose load		Not reported	<p>55% at baseline to 61% after three years in the placebo group (P=0.003) and from 54% to 55% in the metformin group (P>0.2), but decreased in the intensive lifestyle group from 51 to 43% (P<0.001).</p> <p>Three-year cumulative incidences of the metabolic syndrome were 51% for placebo, 45% for metformin, and 34% for intensive lifestyle groups.</p> <p>Secondary: Not reported</p>
<p>Diabetes Prevention Program Research Group¹²⁸ (2015)</p> <p>Metformin 850 mg BID</p> <p>vs</p> <p>placebo with standard lifestyle recommendations</p> <p>vs</p> <p>intensive lifestyle modifications designed to achieve and maintain a 7% weight loss and 150 minutes of exercise a week</p>	<p>DB, MC, PC, RCT</p> <p>Nondiabetic patients ≥25 years of age at high risk with elevated fasting and post-load plasma glucose concentrations, BMI ≥24 kg/m² or ≥22 kg/m² for Asian patients, a plasma glucose concentration 95 to 125 mg/dL, and 140 to 199 mg/dL 2 hours after a 75 g oral glucose load</p>	<p>N=2,776</p> <p>15 years (mean)</p>	<p>Primary: Development of diabetes</p> <p>Secondary: Aggregate microvascular disease (including nephropathy, retinopathy, and neuropathy)</p>	<p>Primary: Diabetes incidence rates after an average follow-up of 15 years were significantly lower by 27 and 18% with lifestyle intervention (HR, 0.73; CI, 0.65 to 0.83) and metformin (HR, 0.82; CI, 0.72 to 0.93), respectively, compared with the placebo group.</p> <p>Secondary: The average prevalence of the microvascular outcomes did not differ significantly among the three treatment groups, despite the group differences in diabetes incidence. However, in women (n=1,887) lifestyle intervention was associated with a lower prevalence (8.7%) than in the placebo (11%) and metformin (11.2%) groups, with 21% (P=0.03) and 22% (P=0.02) reductions with lifestyle compared with placebo and metformin, respectively. Compared with participants who progressed to diabetes, those who didn't progress had a 28% lower prevalence of microvascular complications (P<0.0001).</p>
Zinman et al. ¹²⁹ CANOE	DB, RCT Patients with	N=207 3.9 years	Primary: Time to development of	Primary: Incident diabetes occurred in significantly fewer patients receiving combination therapy compared to placebo (14 vs 39%; P<0.0001). The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Rosiglitazone 2 mg/day plus metformin 500 mg BID</p> <p>vs</p> <p>placebo</p>	<p>impaired glucose tolerance</p>	<p>(median duration)</p>	<p>diabetes</p> <p>Secondary: Insulin sensitivity, β cell function, safety</p>	<p>relative risk reduction was 66% (95% CI, 48 to 80) and the absolute risk reduction was 26% (95% CI, 14 to 37), yielding a number needed to treat of 4 (95% CI, 2.70 to 7.14).</p> <p>Seventy patients (80%) receiving combination therapy regressed to normal glucose tolerance compared to 52 patients (53%) receiving placebo (P=0.0002).</p> <p>Secondary: Insulin sensitivity decreased by trial end in patients receiving placebo (median, -1.24) and remained unchanged in patients receiving combination therapy (median, -0.39; P=0.0006 vs placebo).</p> <p>Change in β cell function did not differ between the two treatments (P=0.28).</p> <p>Significantly more patients receiving combination therapy experienced diarrhea compared to placebo (P=0.0253).</p>
<p>Van de Laar et al.¹³⁰ (2006)</p> <p>Metformin</p> <p>vs</p> <p>acarbose, placebo, diet and exercise, or both</p>	<p>MA (5 trials)</p> <p>Patients with impaired glucose tolerance or impaired fasting blood glucose</p>	<p>N=2,360</p> <p>1 to 6 years</p>	<p>Primary: Occurrence of type 2 diabetes</p> <p>Secondary: Cardiovascular morbidity and mortality, glycemic control, lipids, BP, body weight</p>	<p>Primary: In the comparison of acarbose to placebo, the incidence of or conversion to type 2 diabetes was reduced (RR, 0.78; 95% CI, 0.68 to 0.90).</p> <p>Neither acarbose nor metformin had significant effects on the incidence of type 2 diabetes when compared to one another. However, when compared to diet and exercise, acarbose had beneficial effects on the incidence of type 2 diabetes (RR, 0.40; 95% CI, 0.17 to 0.96).</p> <p>Secondary: There were no significant effects on total mortality or mortality due to cardiovascular causes in trials comparing acarbose to placebo. In one trial (STOP-NIDDM), a decreasing effect on the incidence of cardiovascular disease as a combined end point (MI, angina, revascularization procedures, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease) was reported (RR, 0.47; 95% CI, 0.26 to 0.86).</p> <p>Acarbose decreased PPG by 0.61 mmol/L (95% CI, 0.27 to 0.95)</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>compared to placebo. In the EDIT study, acarbose significantly decreased FPG and PPG in comparison to placebo (P=0.0043 and P=0.0075, respectively). In comparison to metformin, acarbose showed a decreasing effect on PPG (1.40 mmol/L; 95% CI, 0.55 to 2.25). Similarly, acarbose vs diet and exercise also showed significant reductions in FPG and PPG (-1.37 [95% CI, -0.50 to -2.24] and -2.79 mmol/L [95% CI, -1.79 to -3.79]).</p> <p>There were no significant effects on DBP and SBP in trials comparing acarbose to placebo. However, metformin showed significant decreases in both TC and DBP in comparison to acarbose (0.90 mmol/L [95% CI, 0.19 to 1.61] and 6 mm Hg [95% CI, 2.81 to 9.19], respectively).</p> <p>Acarbose decreased body weight by 1.2 kg (95% CI, 0.5 to 1.8) and BMI by 0.3 kg/m² (95% CI, 0.1 to 0.5) compared to placebo.</p>
<p>Salpeter et al.¹³¹ (2008)</p> <p>Metformin (variable doses)</p> <p>vs</p> <p>placebo or no treatment</p>	<p>MA (31 RCTs)</p> <p>Patients at risk for type 2 diabetes mellitus</p>	<p>N=4,570</p> <p>Duration varied</p>	<p>Primary: BMI, fasting glucose, fasting insulin, calculated insulin resistance, HDL-C, LDL-C, TG, incidence of new-onset diabetes</p> <p>Secondary: Not reported</p>	<p>Primary: Pooled results showed that metformin reduced BMI (-5.3%; 95% CI, -6.7 to -4.0), fasting glucose (-4.5%; 95% CI, -6.0 to -3.0), fasting insulin (-14.4%; 95% CI, -19.9 to -8.9), insulin resistance (-22.6%; 95% CI, -27.3 to -18.0), TG (-5.3%; 95% CI, -10.5 to -0.03), and LDL-C (-5.6%; 95% CI, -8.3 to -3.0%), and increased HDL-C (5.0%; 95% CI, 1.6 to 8.3) compared to placebo or no treatment.</p> <p>The incidence of new-onset diabetes was reduced by 40% (OR, 0.6; 95% CI, 0.5 to 0.8), with an absolute risk reduction of 6% (95% CI, 4 to 8) during a mean trial duration of 1.8 years.</p> <p>Secondary: Not reported</p>
Gestational Diabetes				
<p>Moore et al.¹³² (2010)</p> <p>Metformin 500 to 2,000 mg daily (divided doses)</p> <p>vs</p>	<p>DB, PG, RCT</p> <p>Women with gestational diabetes between 11 and 33 weeks gestation at the time of randomization</p>	<p>N=149</p> <p>Variable duration</p>	<p>Primary: Glycemic control</p> <p>Secondary: Medication failure rate, macrosomia, admission to the neonatal intensive</p>	<p>Primary: There was no difference between the glyburide or metformin groups in mean fasting (P=0.23) or two-hour PPG concentrations (post-breakfast, P=0.15; post-lunch, P=0.28; post-dinner, P=0.32).</p> <p>Secondary: Twenty-six patients (34.7%) in the metformin group and 12 patients (16.2%) in the glyburide group did not meet glycemic goals and required</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>glyburide 2.5 to 10 mg BID</p> <p>Insulin was started in treatment failures and oral medication was discontinued.</p>			<p>care unit, five-minute Apgar score less <7, birth trauma, preeclampsia, maternal and neonatal hypoglycemia, and route of delivery</p>	<p>insulin therapy (P=0.01). The failure rate of metformin was 2.1 times higher than the failure rate of glyburide (95% CI, 1.2 to 3.9, OR, 2.7).</p> <p>Macrosomia occurred in 5.4% of patients in the glyburide group and 1.3% of patients in the metformin group (P=0.20). The mean birth weight of babies in the metformin group was smaller than the mean birth weight of babies in the glyburide group (P=0.02). Other neonatal outcomes did not differ between the two groups.</p> <p>There were four neonatal intensive care unit admissions in the metformin group and one neonatal intensive care unit admission in the glyburide group (P=0.37).</p> <p>There were no 5-minute Apgar scores <7 in either group.</p> <p>There was one shoulder dystocia in the glyburide group and one third-degree tear in the metformin group (P=0.49).</p> <p>The incidence of maternal hypoglycemia and preeclampsia was not different between the two treatment groups (P=0.56 and P>0.50, respectively). One infant in the metformin group experienced hypoglycemia with blood glucose less than 40 mg/dL.</p> <p>Excluding elective repeat cesarean deliveries, there were 11 cesarean deliveries in the metformin group compared with two cesarean deliveries in the glyburide group (P=0.02).</p>
<p>Ibrahim et al.¹³³ (2013)</p> <p>Group I: oral metformin (500 mg TID) without increasing the insulin dose</p> <p>vs</p>	<p>NI, RCT</p> <p>Pregnant women with gestational or pre-existing DM at gestations between 20 and 34 weeks who showed insulin resistance (defined as poor glycemic control at</p>	<p>N=90</p> <p>Variable duration</p>	<p>Primary: Maternal glycemic control</p> <p>Secondary: Maternal hypoglycemia, hospital admissions, neonatal outcomes</p>	<p>Primary: Glycemic control was achieved in 76.1% of patients in group I and 100% of patients in group II (P=0.001).</p> <p>Secondary: Readmission for poor glycemic control was not significantly different between groups (P=0.471). Bouts of maternal hypoglycemia occurred in 6.5% of patients in group I and 22.7% in group II (P=0.029).</p> <p>Only two neonatal/delivery outcomes showed a statistical difference: Neonatal hypoglycemia occurred in 7.0% of cases in group I vs 38.5% in</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
group II: increased insulin dose	a daily dose of ≥ 1.12 units/kg			group II (P=0.001). Neonatal Intensive Care Unit admission occurred in 18.6% of group I neonates and 41% of group II neonates (P=0.026).
Spaulonci et al. ¹³⁴ (2013) Metformin vs insulin	PRO, RCT Women with gestational diabetes with singleton pregnancy, use of diet and exercise for a minimum period of 1 week without satisfactory glycemic control, absence of risk factors for lactic acidosis, and absence of anatomic and/or chromosome anomalies of the conceptus detected by ultrasonography.	N=92 Variable duration	Primary: Maternal glycemic control Secondary: Neonatal outcomes	Primary: Higher mean glucose levels were observed in the insulin group (P=0.020), mainly because of higher levels observed after dinner (P=0.042). Twenty-one percent of women using insulin and 27% of women using metformin achieved adequate glycemic control in the first week of treatment (P=0.11). Twelve (26.08%) of the 46 women in the metformin group required supplemental insulin for adequate glycemic control. Secondary: No significant differences between the two groups were observed regarding the following neonatal outcomes: gestational age at birth, 1-minute Apgar score, 5-minute Apgar score, umbilical artery pH at birth, or newborn weight. There were no fetuses with macrosomia in the group metformin vs three (6.5%) cases in the insulin group (P=0.242). A higher frequency of neonatal hypoglycemia was observed in cases treated with insulin (22.2%) compared with newborns from the metformin group (6.5%) (P=0.032).
Niromanesh et al. ¹³⁵ (2012) Metformin vs insulin	RCT, SB Gestational diabetes mellitus women with singleton pregnancy and gestational age between 20 and 34 weeks who did not achieve glycemic control on diet	N=160 Variable duration	Primary: Maternal glycemic control, birth weight Secondary: Neonatal and obstetric complications	Primary: The two groups were comparable with respect to mean fasting blood sugar and postprandial measurements throughout pregnancy after randomization until delivery. The mean fasting blood sugar was <95 mg/dL in 74% and 79% of women in the metformin and insulin groups, respectively (P=0.457). Neonates from the metformin group had a significantly lower circumference of head, arm and chest (P<0.05) and had lower birth weight (P=0.005) and height (P=0.033). The frequency rate of SGA (small for gestational age; birth weight < 10th percentile) was 3.8% in the metformin group and 2.5% in the insulin group. The relative risk of LGA (large for gestational age; birth weight > 90th percentile) in the metformin group was half that of the insulin group (RR, 0.5; 95% CI, 0.3 to 0.9, P=0.012). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>The relative risk of emergency cesarean and preterm delivery was 1.6 and 2.2 times higher, respectively, in the metformin group; however, this was not statistically significant. The two groups were not statistically different in terms of need for phototherapy, incidence of hypoglycemia, and birth defects. The two groups were comparable with respect to umbilical artery pH, Apgar score at 5 min, and hospitalization days. Neonatal Intensive Care Unit admission and respiratory distress syndrome was nonsignificantly more frequent in the metformin group (RR, 2.5; 95% CI, 0.5 to 12.5, P=0.443).</p>
<p>Poolsup et al.¹³⁶ (2014)</p> <p>Pool A: metformin vs insulin</p> <p>Pool B: glyburide vs insulin</p>	<p>MA</p> <p>Women with gestational diabetes mellitus</p>	<p>N=2,151 (13 RCTs)</p> <p>Variable duration</p>	<p>Primary: Safety and efficacy of oral antidiabetic agents compared to insulin</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p><u>Pool A</u></p> <p>There was a nonsignificant difference in the risk of macrosomia (RR, 0.93; 95% CI, 0.61 to 1.41) and large for gestational age (LGA) births (RR, 0.88; 95% CI, 0.70 to 1.12) between the two study groups. A significant increase in the risk of preterm births occurred in the metformin group as compared to insulin (RR, 1.51; 95% CI, 1.04 to 2.19; P=0.03). Rate of neonatal/perinatal mortality was very low in both groups and results remained statistically non-significant. Risk of shoulder dystocia, neonatal hypoglycemia, congenital abnormality, and small for gestational age (SGA) births tended to be lower with metformin but statistical significance was not achieved. A non-significant decrease in risk of caesarean section, pre-eclampsia, and labor induction was noticed with metformin compared to insulin. A significant decrease in the risk of gestational hypertension was observed in the metformin arm (RR, 0.54; 95% CI, 0.31 to 0.91; P=0.02). A significant decrease in PPG levels occurred (mean difference, -2.47 mg/dL; 95% CI, -4.00 to -0.94, P=0.002) in metformin group compared to insulin, while results were statistically nonsignificant between the two groups for FPG levels (mean difference, 0.74 mg/dL; 95% CI, -0.52 to -2.01).</p> <p><u>Pool B</u></p> <p>Glyburide significantly increased the risk of macrosomia (RR, 3.07; 95% CI, 1.14 to 8.23; P=0.03) and neonatal hypoglycemia (RR, 2.30; 95% CI, 1.28 to 4.11; P=0.005) compared to insulin. There was no difference between glyburide and insulin with regard to risk for LGA births; statistically significant heterogeneity was detected for this outcome. There were no significant differences in the risk of preterm births, neonatal</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>mortality, congenital abnormality, or SGA births for glyburide versus insulin. None of the maternal outcomes (caesarean section, pre-eclampsia, maternal hypoglycemia, glycemic levels) displayed a significant difference between glyburide and insulin. The effect estimate for fasting glucose levels (mean difference, 1.90 mg/dL; 95% CI, -0.38 to 4.18) and postprandial glucose levels (mean difference, 3.42 mg/dL; 95% CI, -1.17 to 8.02) favored the insulin group, but results remained nonsignificant.</p> <p>Secondary: Not reported</p>

*Synonym for glyburide.

†Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily, QID=four times daily, SC=subcutaneous, TID=three times daily, XR=extended-release
 Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PM=post-marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, SR=systematic review, XO=cross-over
 Miscellaneous abbreviations: apo=apolipoprotein, AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta cell function, HOMA-S=homeostasis model assessment-insulin sensitivity, HR=hazard ratio, IU=international units, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral protamine Hagedorn, NYHA=New York Heart Association, OR=odds ratio, PPG=postprandial plasma glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TNF=Tumor necrosis factor, TZD=thiazolidinedione, WMD=weighted mean difference

Additional Evidence

Dose Simplification

Schwartz et al. compared the efficacy, tolerability, and safety of metformin immediate-release tablets and metformin extended-release tablets. Patients received a dose of 1,500 mg once daily, 1,500 mg twice daily, or 2,000 mg once daily of metformin extended-release or 1,500 mg daily of metformin immediate-release given in two divided doses. The investigators demonstrated that once-daily extended-release metformin was as effective as twice-daily immediate-release metformin.²⁴

Donnan et al. evaluated the patterns and predictors of adherence in patients with type 2 diabetes receiving treatment with a single antidiabetic agent. Adherence was $\geq 90\%$ in 31.3% of the patients prescribed sulfonylureas and 33.9% of patients prescribed metformin. Patients with better adherence tended to be younger and had a shorter duration of diabetes. There were linear trends of poorer adherence with each increase in the daily number of tablets taken for both sulfonylurea ($P=0.001$) and metformin ($P=0.074$) indices. There were significant trends of decreasing adherence with the number of co-medications for the sulfonylurea group ($P=0.0001$) and metformin group ($P=0.007$). This study did not measure the impact of adherence on clinical outcomes.¹³⁷

Stable Therapy

Fujioka et al. evaluated glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation. The investigators found comparable efficacy and tolerability among the treatment groups.²³ Bhansali et al. demonstrated similar results when patients were switched from an immediate-release metformin product to an extended-release product. The investigators found that patients receiving immediate-release metformin achieved comparable glycemic control when treatment was switched to a once- or twice-daily metformin extended-release product.²¹

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 11. Relative Cost of the Biguanides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Metformin	Extended-release tablet, solution, tablet	Fortamet [®] *, Glucophage [®] *, Glucophage XR [®] *, Glumetza [®] *, Riomet [®]	\$\$\$\$\$	\$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Metformin is the only biguanide that is currently available and it is approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹⁻⁴ The immediate-release and sustained-release tablets are both available in a generic formulation.

According to current clinical guidelines, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin (HbA_{1c}) will most likely require combination or triple therapy in order to achieve glycemic goals, and at this time, there are no uniform recommendations on the best agent to be combined with metformin. Metformin may be considered for the prevention/delay of type 2 diabetes in certain patients. Furthermore, metformin is recommended first-line, and should be initiated at the time of diagnosis, along with lifestyle modifications, unless contraindicated. Metformin is recognized as having high HbA_{1c}-lowering potential, a low risk of hypoglycemia, and a weight neutral effect compared to other available antidiabetic medications. Among all current clinical guidelines, no one metformin formulation is recommended or preferred over another.⁷⁻¹⁹

Numerous clinical trials have established the efficacy/safety of metformin as monotherapy, as well as in combination with other antidiabetic agents.²⁰⁻¹³⁵ Studies directly comparing immediate-release and sustained-release formulations of metformin have demonstrated similar efficacy.²¹⁻²³

The most common adverse events with metformin are gastrointestinal in nature and include diarrhea, flatulence, nausea/vomiting, abdominal discomfort and indigestion. There is also a risk of lactic acidosis with metformin. Although it occurs rarely, it can be fatal in approximately 50% of cases. Patients with renal insufficiency, congestive heart failure, hepatic impairment, history of lactic acidosis, decreased tissue perfusion, hemodynamic instability, hypoxic states or serious acute illness are at increased risk of lactic acidosis.¹⁻⁴

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin.¹⁻⁴

There is insufficient evidence to support that one brand biguanide is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand biguanide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Fortamet® [package insert]. Atlanta (GA): Sciele Pharma Inc.; 2008 Jul.
2. Glucophage® and Glucophage XR® [package insert]. Princeton (NJ): Bristol-Myers Squibb Company; 2008 Sep.
3. Glumetza® [package insert]. Menlo Park (CA): Depomed, Inc.; 2011 Apr.
4. Riomet® [package insert]. Jacksonville (FL): Ranbaxy Laboratories Inc.; 2010 Dec.
5. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Jan]. Available from: <http://www.thomsonhc.com/>.
6. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Jan 2017]. Available from: <http://online.factsandcomparisons.com>.
7. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2016;39(Suppl. 1):S1–S112.
8. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015 Mar;58(3):429-42.
9. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.
10. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1:1-87..
11. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. Endocr Pract. 2016;22(1):84-113..
12. National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes. [guideline on the Internet]. London: NICE; 2009 May [cited 2014 Oct]. Available from: <http://www.nice.org.uk/guidance/cg87>.
13. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
14. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
15. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
16. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131(2):364-382.
17. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.
18. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.
19. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care 2014;37(7):2034-2054.
20. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes. Diabetes Care. 2002 Jan;25(1):89-94.
21. Bhansali A, Masoodi SR. Efficacy of once- or twice-daily extended release metformin compared with thrice-daily immediate release metformin in type 2 diabetes mellitus. J Assoc Physicians India. 2005 May;53:441-5.
22. Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. Curr Med Res Opin. 2004 Apr;20(4):565-72.

23. Fujioka K, Pans M, Joyal S. Glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation. *Clin Ther.* 2003 Feb;25(2):515-29.
24. Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, Lewin A. Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. *Diabetes Care.* 2006 Apr;29(4):759-64.
25. Pavo I, Jermendy G, Varkonyi TT, Kerenyi Z, Gyimesi A, Shoustov S, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2003 Apr;88(4):1637-45.
26. Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel B. Comparative outcomes study of metformin intervention versus conventional approach. *Diabetes Care.* 2005 Mar;28(3):539-43.
27. Gottschalk M, Danne T, Vlajnic A, Cara JF. Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes. *Diabetes Care.* 2007 Apr;30(4):790-4.
28. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care* 2013;36:1301-1311.
29. Lund SS, Tarnow L, Stehouwer CD, Schalkwijk CG, Teerlink T, Gram J, Winther K, Frandsen M, Smidt UM, Pedersen O, Parving HH, Vaag AA. Impact of metformin versus repaglinide on non-glycaemic cardiovascular risk markers related to inflammation and endothelial dysfunction in non-obese patients with type 2 diabetes. *Eur J Endocrinol.* 2008 May;158(5):631-41.
30. Lund SS, Tarnow L, Frandsen M, Smidt UM, Pedersen O, Parving HH, Vaag AA. Impact of metformin versus the prandial insulin secretagogue, repaglinide, on fasting and postprandial glucose and lipid responses in non-obese patients with type 2 diabetes. *Eur J Endocrinol.* 2008 Jan;158(1):35-46.
31. Fang FS, Gong YP, Li CL, Li J, et al. Comparison of repaglinide and metformin monotherapy as an initial therapy in Chinese patients with newly diagnosed type 2 diabetes mellitus. *European Journal of Endocrinology* 2014;170:901-908.
32. Sullivan D, Forder P, Simes J, Whiting M, Kritharides L, Merrifield A, et al. Associations between the use of metformin, sulphonylureas, or diet alone and cardiovascular outcomes in 6005 people with type 2 diabetes in the FIELD study. *Diabetes Research and Clinical Practice.* 2011;9:284-90.
33. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006 Mar 29;355:2427-43.
34. Aschner P, Katzeff HL, Guo H, et al. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. *Diabetes Obes Metab* 2010;12:252-61.
35. Nichols GA, Gomez-Caminero A. Weight changes following the initiation of new anti-hyperglycemic therapies. *Diabetes Obes Metab.* 2007 Jan;9(1):96-102.
36. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzolez JG, Chan M, et al. Efficacy and safety of exenatide once weekly vs metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4). *Diabetes Care.* 2012;35:252-8.
37. Simpson SH, Majumdar SR, Tsuyuki RT, et al. Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. *CMAJ.* 2006;174(2):169-74.
38. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al; Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med.* 2007 Sep;147(6):428-30.
39. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005 Jul 20;(3):CD002966.
40. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract.* 2008 Feb;79(2): 196-203.
41. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes. *JAMA.* 2007;298(2):194-206.
42. Frederich R, Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. *Postgrad Med.* 2010 May;122(3):16-27.
43. Singh S, Loke YK, Furberg CD. Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systemic review and meta-analysis. *Thorax.* 2011;66:383-8.
44. Louisa M, Takeuchi M, Nafrialdi, Setiabudy R. A meta-analysis on treatment effects of thiazolidinediones for type 2 diabetes mellitus in Asian populations. *Acta Med Indones.* 2011 Jan;43(1):39-52.
45. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2006 Oct 18;(4):CD006060.

46. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA*. 2007 Sep 12;298(10):1180-8.
47. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. *Lancet*. 2007 Sep 29;370:1129-36.
48. Mannucci E, Monami M, Lamanna C, Gensini GF, Marchionni N. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2008;10:1221-38.
49. Nagajothi N, Adigopula S, Balamuthusamy S, Velazquez-Cecena JL, Raghunathan K, Khraisat A, et al. Pioglitazone and the risk of myocardial infarction and other major adverse cardiac events: a meta-analysis of randomized, controlled trials. *Am J Ther*. 2008;15:506-11.
50. Karter AJ, Ahmed AT, Liu J, Moffet HH, Parker MM. Pioglitazone initiation and subsequent hospitalization for congestive heart failure. *Diabetic Med*. 2005 Aug;22:986-93.
51. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA*. 2007 Sep 12;298(10):1189-95.
52. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457-71.
53. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007 Jul 18;(3):CD006063.
54. Kheirbek RE, Alemi F, Zargoush M. Comparative effectiveness of hypoglycemic medications among veterans. *J Manag Care Pharm*. 2013;19(9):740-44.
55. Halimi S, Le Berre MA, Grange V. Efficacy and safety of acarbose add-on therapy in the treatment of overweight patients with type 2 diabetes inadequately controlled with metformin: a double-blind, placebo-controlled study. *Diabetes Res Clin Pr*. 2000;50(1):49-56.
56. Phillips P, Karrasch J, Scott R, et al. Acarbose improves glycemic control in overweight type 2 diabetic patients insufficiently treated with metformin. *Diabetes Care*. 2003;26(2):269-73.
57. Rosenstock J, Chuck L, González-Ortiz M, et al. Initial Combination Therapy With Canagliflozin Plus Metformin Versus Each Component as Monotherapy for Drug-Naïve Type 2 Diabetes. *Diabetes Care*. 2016 Mar;39(3):353-62.
58. Lopez-Alvarenga JC, Aguilar-Salinas CA, Velasco-Perez ML, et al. Acarbose vs bedtime NPH insulin in the treatment of secondary failures to sulphonylurea-metformin therapy in type 2 diabetes mellitus. *Diabetes Obes Metab*. 1999;1(1):29-35.
59. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin improves glycemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab*. 2012;14:565-74.
60. Haak T, Meinicke T, Jones R, et al. Initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomised, double-blind 1-year extension study. *Int J Clin Pract* 2013;67(12):1283–1293.
61. Standl E, Schernthaner G, Rybka J, et al. Improved glycemic control with miglitol in inadequately-controlled type 2 diabetics. *Diabetes Res Clin Pr*. 2001;51(3):205-13.
62. Van Gaal L, Maislos M, Schernthaner G, et al. Miglitol combined with metformin improves glycemic control in type 2 diabetes. *Diabetes Obes Metab*. 2001;3(5):326-31.
63. Chiasson J, Naditch L. The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. *Diabetes Care*. 2001;24(6):989-94.
64. DeFronzo R, Hissa M, Garber A, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care* 2009;32:1649-1655.
65. Hermans MP, Delibasi T, Farmer I, et al. Effects of saxagliptin added to sub-maximal doses of metformin compared with uptitration of metformin in type 2 diabetes: the PROMPT study. *Current Medical Research & Opinion* 2012;28(10):1635-1645.
66. Pfützner A, Paz-Pacheco E, Allen E, Frederich R, Chen R; CV181039 Investigators. Initial combination therapy with saxagliptin and metformin provides sustained glycemic control and is well tolerated for up to 76 weeks. *Diabetes Obes Metab*. 2011 Jun;13(6):567-76.
67. Jadzinsky M, Pfützner A, Paz-Pacheco E, et al. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes Obes Metab* 2009;11:611-22.

68. Derosa G, Maffioli P, Salvadeo SAT, Ferrari I, Ragonesi PD, Querci F, et al. Effects of sitagliptin or metformin added to pioglitazone monotherapy in poorly controlled type 2 diabetes mellitus patients. *Metabolism Clinical and Experimental*. 2010;59:887-95.
69. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE Sitagliptin 036 Study Group. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2007 Aug;30(8):1979-87.
70. Reasner C, Olansky L, Seck TL, Williams-Herman DE, Terranella L, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared to metformin monotherapy in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2011 Jul;13(7):644-52.
71. Raz I, Chen Y, Wu M, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. *Curr Med Res Opin*. 2008;24:537-550.
72. Derosa G, Carbone A, Franzaetti I, et al. Effects of a combination of sitagliptin plus metformin vs metformin monotherapy on glycemic control, β -cell function and insulin resistance in type 2 diabetic patients. *Diabetes Research and Clinical Practice* 2012;98:51-60.
73. Perez-Monteverde A, Seck T, Xu L, Lee MA, Sisk CM, Williams-Herman DE, et al. Efficacy and safety of sitagliptin and fixed-dose combination of sitagliptin and metformin vs pioglitazone in drug-naïve patients with type 2 diabetes. *Int J Clin Pract*. 2011 Sep;65(9):930-8.
74. Wainstein J, Katz L, Engel SS, Xu L, Golm GT, Hussain S, et al. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism*. 2012;14:409-18.
75. Scott R, Loeys T, Davies M, Engel S. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2008;10:959-969.
76. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab*. 2007 Sep;9(5):733-45.
77. Rigby SP, Handelsman Y, Lai YL, et al. Effects of colesevelam, rosiglitazone, or sitagliptin on glycemic control and lipid profile in patients with type 2 diabetes mellitus inadequately controlled by metformin monotherapy. *Endocr Pract* 2010;16:53-63.
78. Douek IF, Allen SE, Ewings P, Gale EA, Bingley PJ; the Metformin Trial Group. Continuing metformin when starting insulin in patients with type 2 diabetes: a double-blind randomized placebo-controlled trial. *Diabet Med*. 2005 May;22(5):634-40.
79. Wulffelé MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der Burg B, et al. Combination of insulin and metformin in the treatment of type 2 diabetes. *Diabetes Care*. 2002 Dec;25(12):2133-40.
80. Yki-Järvinen H, Kauppinen-Mäkelin RK, Tiikkainen M, Vähätalo M, Virtamo H, Nikkilä K, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia*. 2006 Mar;49(3):442-51.
81. Horton E, Clinkingbeard C, Gatlin M, et al. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care*. 2000;23(11):1660-5.
82. Marre M, Van Gaal L, Usadel K-H, et al. Nateglinide improves glycemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. *Diabetes Obes Metab*. 2002;4(3):177-86.
83. Raskin P, Klaff L, Mill J, et al. Efficacy and safety of combination therapy repaglinide plus metformin versus nateglinide plus metformin. *Diabetes Care*. 2003;26(7):2063-8.
84. Gerich J, Raskin P, Jean-Louis L, et al. PRESERVE- β Two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. *Diabetes Care*. 2003;28(9):2093-9.
85. Schwarz SL, Gerich JE, Marcellari A, et al. Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naïve elderly patients with type 2 diabetes. *Diabetes Obes Metab*. 2008; 10(8): 652-60.
86. Derosa G, D'Angelo A, Fogari E, et al. Nateglinide and glibenclamide metabolic effects in naïve type 2 diabetic patients treated with metformin. *J Clin Pharm Ther* 2009;34: 13-23.
87. Wang W, Bu R, Su Q, Liu J, Ning G. Randomized study of repaglinide alone and in combination with metformin in Chinese subjects with type 2 diabetes naïve to oral antidiabetes therapy (abstract). *Expert Opin Pharmacother*. 2011 Dec;12(18):2791-9.
88. Moses R, Slobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 1999;22(1):119-24.

89. Civera M, Merchante A, Salvador M, Sanz J, Martínez I. Safety and efficacy of repaglinide in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes. *Diabetes Res Clin Pract.* 2008 Jan;79(1):42-7. Epub 2007 Aug 21.
90. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogs for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2007 Apr 18;(2):CD004654.
91. Bayraktar M, Van Thiel D, Adalar N. A comparison of acarbose versus metformin as an adjuvant therapy in sulfonylurea-treated NIDDM patients. *Diabetes Care.* 1996;19(3):252-4.
92. Abbasi F, Chu JW, McLaughlin T, Lamendola C, Leary ET, Reaven GM. Effect of metformin treatment on multiple cardiovascular disease risk factors in patients with type 2 diabetes mellitus. *Metabolism.* 2004 Feb;53(2):159-64.
93. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med.* 1995 Aug;333(9):541-9.
94. Goldstein BJ, Pans M, Rubin CJ. Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. *Clin Ther.* 2003;25(3):890-903.
95. Garber AJ, Larsen L, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab.* 2002;4(3):201-8.
96. Marre M, Howlett H, Lehert P, et al. Improved glycemic control with metformin-glibenclamide combined tablet therapy (Glucovance®) in type 2 diabetic patients inadequately controlled on metformin. *Diabet Med.* 2002;19(8):673-80.
97. Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. *Diabet Med.* 2005 Apr;22:497-502.
98. Hollander P, Sugimoto D, Vlajnic A, Kilo C. Combination therapy with insulin glargine plus metformin but not insulin glargine plus sulfonylurea provides similar glycemic control to triple oral combination therapy in patients with type 2 diabetes uncontrolled with dual oral agent therapy. *J Diabetes Complications.* 2015 Nov-Dec;29(8):1266-71.
99. Duckworth W, Marcelli M, Padden M, et al. Improvements in glycemic control in type 2 diabetes patients switched from sulfonylurea coadministered with metformin to glyburide-metformin tablets. *J Managed Care Pharm.* 2003;9(3):256-62.
100. Blonde L, Wogen J, Kreilick, et al. Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide coadministered with metformin. *Diabetes Obes Metab.* 2003;5(6):424-31.
101. Lewin A, Lipetz R, Wu J, Schwartz S. Comparison of extended-release metformin in combination with a sulfonylurea (glyburide) to sulfonylurea monotherapy in adult patients with type 2 diabetes: a multicenter, double-blind, randomized, controlled, phase III study. *Clin Ther.* 2007 May;29(5):844-55.
102. Chien HH, Chang CT, Chu NF, et al. Effect of glyburide-metformin combination tablet in patients with type 2 diabetes. *J Chin Med Assoc* 2007;70:473-80.
103. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The Pioglitazone 027 Study Group. *Clin Ther.* 2000;22(12):1395-409.
104. Kaku K. Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial. *Curr Med Res Opin* 2009;25:1111-9.
105. Perez A, Zhao Z, Jacks R, et al. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. *Curr Med Res Opin* 2009;25:2915-2923.
106. Seufert J, Urquhart R. 2-year effects of pioglitazone add-on to sulfonylurea or metformin on oral glucose tolerance in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2008;79: 453-60.
107. Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Schernthaner G. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. *Diabetes Metab Res Rev.* 2005;21(2):167-74.
108. Charbonnel B, Schernthaner G, Brunetti P, Matthews DR, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia.* 2005;48(6):1093-104. Epub 2005 May 12.
109. Hanefeld M, Brunetti P, Schernthaner GH, Matthews DR, Charbonnel BH; on behalf of the QUARTET Study Group. *Diabetes Care.* 2004 Jan;27(1):141-7.

110. Comaschi M, Corsi A, Di Pietro C, et al. The effect of pioglitazone as add-on therapy to metformin or sulphonylurea compared to a fixed-dose combination of metformin and glibenclamide on diabetic dyslipidaemia. *Nutr Metab Cardiovasc Dis.* 2008;18:373-9.
111. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes Metab.* 2015 Mar;17(3):268-75.
112. Borges JLC, Bilezikian JP, Jones-Leone AR, Acosta AP, Ambery PD, Nino AJ, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycemc control and bone mineral density after 80 weeks of treatment in drug-naïve type 2 diabetes mellitus patients. *Diabetes, Obesity and Metabolism.* 2011;13:1036-46.
113. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. *JAMA.* 2000;283:1695-702.
114. Weissman P, Goldstein BJ, Rosenstock J, Waterhouse B, Cobitz AR, Wooddell MJ, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE study. *Curr Med Res Opin.* 2005 Dec;21(12):2029-35.
115. Stewart MW, Cirkel DT, Furuseth K, Donaldson J, Biswas N, Starkie MG, et al. Effect of metformin plus rosiglitazone compared with metformin alone on glycemc control in well-controlled type 2 diabetes. *Diabet Med.* 2006 Oct;23:1069-78.
116. Rosak C, Petzoldt R, Wolf R, Reblin T, Dehmel B, Seidel D. Rosiglitazone plus metformin is effective and well tolerated in clinical practice: results from large observational studies in people with type 2 diabetes. *Int J Clin Pract.* 2005;59(10):1131-6.
117. Bailey CJ, Bagdonas A, Rubes J, McMorn SO, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. *Clin Ther.* 2005;27(10):1548-61.
118. Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. *Diabetes Obes Metab.* 2006;8:650-60.
119. TODAY Study Group. A clinical trial to maintain glycemc control in youth with type 2 diabetes. *N Engl J Med.* 2012;366:2247-56.
120. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, Komajda M, et al; for the RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes-an interim analysis. *N Engl J Med.* 2007;357(1):28-38.
121. Home P, Pocock S, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;373:2125-35.
122. Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. *Am Heart J.* 2013;166(2):240-249.
123. Home PD, Jones NP, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, et al; for the RECORD Study Group. Rosiglitazone RECORD study: glucose control outcomes at 18 months. *Diabet Med.* 2007;24:626-34.
124. Komajda M, Curtis P, Hanefeld M, et al. Effect of the addition of rosiglitazone to metformin or sulphonylureas versus metformin/sulphonylurea combination therapy on ambulatory blood pressure in people with type 2 diabetes: a randomized controlled trial (the RECORD study). *Cardiovasc Diabetol.* 2008;7:10.
125. Hamann A, Garcia-Puig J, Paul G, et al. Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with type 2 diabetes inadequately controlled on metformin alone. *Exp Clin Endocrinol Diabetes.* 2008 Jan;116(1): 6-13.
126. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002 Feb;346(6):393-403.
127. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, et al; Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the diabetes prevention program randomized trial. *Ann Intern Med.* 2005 Apr 19;142:611-9.
128. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol.* 2015 Nov;3(11):866-75.

129. Zinman B, Harris SB, Neuman J, Gerstein HC, Retnakaran RR, Raboud J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomized controlled study. *Lancet*. 2010;376:103-11.
130. Van de Laar FA, Lucassen PLBJ, Akkermans RP, Van de Lisdonk EH, De Grauw WJC. Alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose (review). *Cochrane Database Syst Rev*. 2006 Oct 18;(4):CD005061.
131. Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. *Am J Med*. 2008 Feb;121(2):149-57.e2.
132. Moore LE, Clokey D, Rappaport VJ, et al. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. *Obstet Gynecol* 2010;115:55-9.
133. Ibrahim MI, Hamdy A, Shafik A, et al. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. *Arch Gynecol Obstet* 2014; 289:959–965.
134. Spaulonci CP, Bernardes LS, Trindade TC, et al. Randomized trial of metformin vs insulin in the management of gestational diabetes. *Am J Obstet Gynecol* 2013;209:34.e1-7.
135. Niromanesh S, Alavi A, Sharbaf FR, et al. Metformin compared with insulin in the management of gestational diabetes mellitus: A randomized clinical trial.
136. Poolsup N, Suksomboon N, Amin M (2014) Efficacy and Safety of Oral Antidiabetic Drugs in Comparison to Insulin in Treating Gestational Diabetes Mellitus: A Meta-Analysis. *PLoS ONE* 2014;9(10): e109985. doi:10.1371/journal.pone.0109985.
137. Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. *Diabet Med*. 2002 Apr;19(4):279-84.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
AHFS Class 682005
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The dipeptidyl peptidase-4 (DPP-4) inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are human incretin hormones that are released from the small intestine in response to food intake. These hormones have multiple effects on the stomach, liver, pancreas, and brain to control glucose concentrations; however, they are inactivated by the DPP-4 enzyme within minutes. Endogenous GLP-1 levels have been shown to be reduced in patients with type 2 diabetes. The DPP-4 inhibitors slow the inactivation of the incretin hormones and increase their concentration in the bloodstream. This effect enhances glucose-dependent insulin secretion by pancreatic beta cells and suppresses glucagon secretion from pancreatic alpha cells.¹⁻⁴

Alogliptin, linagliptin, saxagliptin, and sitagliptin are also available in combination with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.⁵⁻¹⁰ Alogliptin is also available in combination with pioglitazone, a thiazolidinedione. The thiazolidinediones increase the insulin sensitivity of adipose tissue, skeletal muscle, and the liver. This results in increased glucose uptake and metabolism, suppression of hepatic glucose production, and decreased plasma free fatty acid concentrations.¹¹ In general, all of the combination DPP-4 inhibitor products are available for use when treatment with both drug components is appropriate.⁵⁻¹¹

The DPP-4 inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. **Alogliptin and alogliptin combination products are available in a generic formulation; metformin and pioglitazone are also available generically in a separate formulation.** This class was last reviewed in February 2015.

Table 1. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Alogliptin	tablet	Nesina ^{®*}	none
Linagliptin	tablet	Tradjenta [®]	none
Saxagliptin	tablet	Onglyza [®]	none
Sitagliptin	tablet	Januvia [®]	Januvia [®]
Combination Products			
Alogliptin and metformin	tablet	Kazano ^{®*}	none
Alogliptin and pioglitazone	tablet	Oseni ^{®*}	none
Linagliptin and metformin	tablet	Jentadueto [®] , Jentadueto XR [®]	none
Saxagliptin and metformin	extended-release tablet	Kombiglyze XR [®]	none
Sitagliptin and metformin	extended-release, tablet, tablet	Janumet [®] , Janumet XR [®]	Janumet [®] , Janumet XR [®]

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Clinical Guideline	Recommendation(s)
<p>American Diabetes Association: Standards of Medical Care in Diabetes (2016)¹²</p>	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <p>Prevention or delay of type 2 diabetes</p> <ul style="list-style-type: none"> An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus. Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p>Glycemic goals in adults</p> <ul style="list-style-type: none"> Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p>Pharmacologic therapy for type 1 diabetes</p> <ul style="list-style-type: none"> Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. Most patients should use of insulin analogs to reduce hypoglycemia risk. Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age.

Clinical Guideline	Recommendation(s)
	<p><u>Pharmacologic therapy for type 2 diabetes</u></p> <ul style="list-style-type: none"> • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If the A_{1c} target is not achieved after approximately three months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • <u>Pregestational Diabetes</u> <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1c} <6.5%, to reduce the risk of congenital anomalies. ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. • <u>Gestational Diabetes Mellitus</u> <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. • <u>General Principles for Management of Diabetes in Pregnancy</u> <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. • Due to increased red blood cell turnover, A_{1c} is lower in normal pregnancy than in normal nonpregnant women. The A_{1c} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: Management of</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.

Clinical Guideline	Recommendation(s)
<p>Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012 and 2015 Update)^{13,14}</p>	<ul style="list-style-type: none"> • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability.

Clinical Guideline	Recommendation(s)																																																																																																																
	<p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. 																																																																																																																
	<p>Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations</p> <table border="1"> <tr> <td>Initial Drug Monotherapy</td> <td colspan="6">Metformin</td> </tr> <tr> <td>Efficacy (↓HbA_{1c})</td> <td colspan="6">High</td> </tr> <tr> <td>Hypoglycemia</td> <td colspan="6">Low risk</td> </tr> <tr> <td>Weight</td> <td colspan="6">Neutral/loss</td> </tr> <tr> <td>Side Effects</td> <td colspan="6">Gastrointestinal/lactic acidosis</td> </tr> <tr> <td colspan="7">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td> </tr> <tr> <td>Two Drug Combinations</td> <td>Metformin + sulfonyl-urea</td> <td>Metformin + thiazolidinedione (TZD)</td> <td>Metformin + DPP-4 inhibitor</td> <td>Metformin + SGLT2 inhibitor</td> <td>Metformin + GLP-1 receptor agonist</td> <td>Metformin + insulin (usually basal)</td> </tr> <tr> <td>Efficacy (↓HbA_{1c})</td> <td>High</td> <td>High</td> <td>Intermediate</td> <td>Intermediate</td> <td>High</td> <td>Highest</td> </tr> <tr> <td>Hypoglycemia</td> <td>Moderate risk</td> <td>Low risk</td> <td>Low risk</td> <td>Low risk</td> <td>Low risk</td> <td>High risk</td> </tr> <tr> <td>Weight</td> <td>Gain</td> <td>Gain</td> <td>Neutral</td> <td>Loss</td> <td>Loss</td> <td>Gain</td> </tr> <tr> <td>Major Side Effects</td> <td>Hypoglycemia</td> <td>Edema, heart failure, bone fracture</td> <td>Rare</td> <td>Genitourinary, dehydration</td> <td>Gastrointestinal</td> <td>Hypoglycemia</td> </tr> <tr> <td colspan="7">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td> </tr> <tr> <td>Three Drug Combinations</td> <td>Metformin + sulfonyl-urea +</td> <td>Metformin + TZD +</td> <td>Metformin + DPP-4 inhibitor +</td> <td>Metformin + SGLT2 inhibitor +</td> <td>Metformin + GLP-1 receptor agonist +</td> <td>Metformin + insulin therapy +</td> </tr> <tr> <td></td> <td>TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin</td> <td>Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin</td> <td>Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin</td> <td>Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin</td> <td>Sulfonyl-urea, TZD, or insulin</td> <td>TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist</td> </tr> <tr> <td colspan="7">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td> </tr> <tr> <td>More Complex Insulin Strategies</td> <td colspan="6">Combination injectable therapy</td> </tr> </table>	Initial Drug Monotherapy	Metformin						Efficacy (↓HbA_{1c})	High						Hypoglycemia	Low risk						Weight	Neutral/loss						Side Effects	Gastrointestinal/lactic acidosis						If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)							Two Drug Combinations	Metformin + sulfonyl-urea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)	Efficacy (↓HbA_{1c})	High	High	Intermediate	Intermediate	High	Highest	Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk	Weight	Gain	Gain	Neutral	Loss	Loss	Gain	Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)							Three Drug Combinations	Metformin + sulfonyl-urea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + SGLT2 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +		TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin	Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin	Sulfonyl-urea, TZD, or insulin	TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist	If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents							More Complex Insulin Strategies	Combination injectable therapy					
Initial Drug Monotherapy	Metformin																																																																																																																
Efficacy (↓HbA_{1c})	High																																																																																																																
Hypoglycemia	Low risk																																																																																																																
Weight	Neutral/loss																																																																																																																
Side Effects	Gastrointestinal/lactic acidosis																																																																																																																
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)																																																																																																																	
Two Drug Combinations	Metformin + sulfonyl-urea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)																																																																																																											
Efficacy (↓HbA_{1c})	High	High	Intermediate	Intermediate	High	Highest																																																																																																											
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk																																																																																																											
Weight	Gain	Gain	Neutral	Loss	Loss	Gain																																																																																																											
Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia																																																																																																											
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)																																																																																																																	
Three Drug Combinations	Metformin + sulfonyl-urea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + SGLT2 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +																																																																																																											
	TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin	Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin	Sulfonyl-urea, TZD, or insulin	TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist																																																																																																											
If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents																																																																																																																	
More Complex Insulin Strategies	Combination injectable therapy																																																																																																																
American College of Physicians: Oral Pharmacologic	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. 																																																																																																																

Clinical Guideline	Recommendation(s)
Treatment of Type 2 Diabetes Mellitus (2012)¹⁵	<ul style="list-style-type: none"> • Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. • It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.
American Association of Clinical Endocrinologists/ American College Of Endocrinology: Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015)¹⁶	<p>Antihyperglycemic pharmacotherapy for type 2 diabetes</p> <ul style="list-style-type: none"> • The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement. • Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. • Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. • Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. • When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. • The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. • When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
American Association of Clinical Endocrinologists: Consensus Statement on the	<p>Principles underlying the algorithm</p> <ul style="list-style-type: none"> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an

Clinical Guideline	Recommendation(s)
<p>Comprehensive Type 2 Diabetes Management Algorithm 2016 (2016)¹⁷</p>	<p>adjunct to it.</p> <ul style="list-style-type: none"> • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • The therapeutic regimen should be as simple as possible to optimize adherence. <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ Sodium glucose cotransporter 2 (SGLT-2) inhibitors. ○ DPP-4 inhibitors. ○ . ○ TZDs (use with caution). ○ Alpha-glucosidase inhibitors. • sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ DPP-4 inhibitors. ○ TZD. ○ Basal insulin. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Three-drug combination therapy</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Insulin therapy algorithm</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <p><u>Basal insulin</u></p> <ul style="list-style-type: none"> • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p><u>Basal-bolus insulin regimens</u></p> <ul style="list-style-type: none"> • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c}

Clinical Guideline	Recommendation(s)
	<p>>10% often respond better to combined basal and mealtime bolus insulin.</p> <ul style="list-style-type: none"> A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. Doses of insulin may be titrated every two to three days to reach glycemic goals. <p><u>Basal insulin and incretin therapy regimens</u></p> <ul style="list-style-type: none"> Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last updated July 2016)¹⁸</p>	<p><u>Individualized care</u></p> <ul style="list-style-type: none"> Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective. Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p><u>HbA_{1c} targets</u></p> <ul style="list-style-type: none"> Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> reinforce advice about diet, lifestyle and adherence to drug treatment and support the person to aim for an HbA_{1c} level of 7.0% and intensify drug treatment. Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job for whom intensive management would not be appropriate, for example, people with significant comorbidities. If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p><u>Drug treatment</u></p> <ul style="list-style-type: none"> For adults with type 2 diabetes, discuss the benefits and risks of drug treatment,

Clinical Guideline	Recommendation(s)
	<p>and the options available. Base the choice of drug treatment(s) on:</p> <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost <ul style="list-style-type: none"> ● If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. ● Initial drug treatment <ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m²: <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p>First intensification of drug treatment</p> <ul style="list-style-type: none"> ● In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. ● In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. ● Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes.

Clinical Guideline	Recommendation(s)
	<p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment. • If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. • Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in six months). • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment. • In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p>Insulin-based treatments</p> <ul style="list-style-type: none"> • When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional. • When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. • Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation. ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if:

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals. ○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes: <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. • Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). • Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)¹⁹</p>	<ul style="list-style-type: none"> • Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes,

Clinical Guideline	Recommendation(s)
	<p>unless medically inappropriate.</p> <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. <ul style="list-style-type: none"> ● Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes (2012)²⁰</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> ● Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. ● Match the timing of medication (including insulin) and meals. ● Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. ● Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals. ● Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. ● Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> ● Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. ● A lower HbA_{1c} target may be considered if it is easily and safely achieved. ● A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> ● Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. ● Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. ● First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. ● Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering mediations (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)²¹</p>	<ul style="list-style-type: none"> • Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations ≥ 250 mg/dL. ○ Whose HbA_{1c} is $>9\%$. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
<p>National Institute for</p>	<p>Education and information for children and young people with type 1 diabetes</p>

Clinical Guideline	Recommendation(s)
<p>Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November 2016)²²</p>	<ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. • Tailor the education programme to each child or young person with type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. • Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Encourage children and young people with type 1 diabetes to wear or carry something that identifies them as having type 1 diabetes (e.g., a bracelet). • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. • Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations. • Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p>Insulin therapy for children and young people with type 1 diabetes</p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. • Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen. • Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. • Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. • Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. • Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin infusion users. • Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. • Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin (0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%. • Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. • Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. • Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with

Clinical Guideline	Recommendation(s)
	<p>type 1 diabetes a review of injection sites at each clinic visit.</p> <ul style="list-style-type: none"> • Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. • If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily injections, continuous subcutaneous insulin infusion [CSII or insulin pump] therapy or once-, twice- or three-times daily mixed insulin injections). <p><u>Oral medicines for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. <p><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. • Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. • Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. • Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain. <p><u>Education and information for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ HbA_{1c} monitoring and targets ○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control ○ the aims of metformin therapy and possible adverse effects ○ the complications of type 2 diabetes and how to prevent them. • Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Explain to children and young people with type 2 diabetes and their family

Clinical Guideline	Recommendation(s)
	<p>members or carers (as appropriate) that like others they are advised to have:</p> <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every 2 years. <ul style="list-style-type: none"> ● Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. ● Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. ● Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible government disability benefits. ● Take particular care when communicating with and providing information to children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. <p><u>Dietary management for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> ● At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. ● Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. ● At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. ● Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications. ● Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. ● Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. ● At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI. ● Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. ● Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy. <p><u>Metformin</u></p> <ul style="list-style-type: none"> ● Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> ● Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. ● Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example,

Clinical Guideline	Recommendation(s)
<p>adults: diagnosis and management (Published 2015; last updated July 2016)²³</p>	<p>if the HbA_{1c} level has risen unexpectedly above a previously sustained target.</p> <ul style="list-style-type: none"> • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles ○ total glycated hemoglobin estimation (if abnormal hemoglobins). • Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. • Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia. • Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p><u>Self-monitoring of blood glucose</u></p> <ul style="list-style-type: none"> • Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least four times a day, including before each meal and before bed. • Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). • Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia. • Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. • Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy) • Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking. <p><u>Continuous glucose monitoring</u></p> <ul style="list-style-type: none"> • Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. • Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously

Clinical Guideline	Recommendation(s)
	<p>preventable precipitating cause.</p> <ul style="list-style-type: none"> ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level ≥9%) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in HbA_{1c} of 2.5% or more. <ul style="list-style-type: none"> ● For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. <p><u>Insulin regimens</u></p> <ul style="list-style-type: none"> ● Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. ● Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only). <p><u>Long-acting insulin</u></p> <ul style="list-style-type: none"> ● Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. ● Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul style="list-style-type: none"> ○ an existing insulin regimen being used by the person that is achieving their agreed targets ○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. ● Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p><u>Rapid-acting insulin</u></p> <ul style="list-style-type: none"> ● Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. ● Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. ● If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. <p><u>Mixed insulin</u></p> <ul style="list-style-type: none"> ● Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. ● Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p><u>Optimizing insulin therapy</u></p> <ul style="list-style-type: none"> ● For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously

Clinical Guideline	Recommendation(s)
	<p>optimized insulin regimen, the following should be considered:</p> <ul style="list-style-type: none"> ○ injection technique ○ injection sites ○ self-monitoring skills ○ knowledge and self-management skills ○ nature of lifestyle ○ psychological and psychosocial difficulties ○ possible organic causes such as gastroparesis. <ul style="list-style-type: none"> ● Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. <p><u>Adjuncts</u></p> <ul style="list-style-type: none"> ● Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> ● Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. ● Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. ● Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. ● After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. ● Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. ● Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. ● Check injection site condition at least annually and if new problems with blood glucose control occur.
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)²⁴</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> ● Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. ● Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. ● If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> ● Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. ● Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after

Clinical Guideline	Recommendation(s)
	<p>exercise.</p> <ul style="list-style-type: none"> • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <p><u>Glycemic control goals</u></p> <ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p> <ul style="list-style-type: none"> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the dipeptidyl peptidase-4 (DPP-4) inhibitors are noted in Table 3.

Table 3. FDA-Approved Indications for the DPP-4 Inhibitors¹⁻¹¹

Generic Name(s)	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults With Type 2 Diabetes	Monotherapy or Combination Therapy as Adjunct to Diet and Exercise to Improve Glycemic Control in Adults With Type 2 Diabetes
Alogliptin		✓
Linagliptin		✓
Saxagliptin		✓
Sitagliptin		✓
Alogliptin and metformin	✓ ^a	
Alogliptin and pioglitazone	✓ ^b	
Linagliptin and metformin	✓ ^c	
Saxagliptin and metformin	✓ ^d	
Sitagliptin and metformin	✓ ^e	

^aWhen treatment with both alogliptin and metformin is appropriate.

^bWhen treatment with both alogliptin and pioglitazone is appropriate.

^cWhen treatment with both linagliptin and metformin or metformin extended-release is appropriate.

^dWhen treatment with both saxagliptin and metformin is appropriate.

^eWhen treatment with both sitagliptin and metformin or metformin extended-release is appropriate.

IV. Pharmacokinetics

The pharmacokinetic parameters of the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the DPP-4 Inhibitors²⁵

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Alogliptin	100	20	Liver, limited (% not reported)	Renal (76), Feces (13)	21
Linagliptin	30	70 to 99	Not reported	Renal (5 to 7), Bile (80)	>100
Saxagliptin	Not reported	Negligible (% not reported)	Liver (% not reported)	Renal (60), Feces (22)	2.5
Sitagliptin	87	38	Liver, minimal (% not reported)	Renal (87), Feces (13)	12.4
Combination Products					
Alogliptin and metformin	100/50 to 60	20/ Negligible (% not reported)	Liver, limited (% not reported)/None	Renal (76), Feces (13)/ Renal (90)	21/6.2
Alogliptin and pioglitazone	100/50*	20/ >99	Liver, limited (% not reported)/ Liver, extensive (% not reported)	Renal (76), Feces (13)/ Renal (15 to 30)	21/3 to 7
Linagliptin and	30/50 to 60	70 to 99/ Negligible (% not	Minimal (% not reported)/None	Renal (5 to 7), Bile (80)/	>100/6.2

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
metformin		reported)		Renal (90)	
Saxagliptin and metformin	Not reported/ 50 to 60	Negligible (% not reported)/ Negligible (% not reported)	Liver (% not reported)/None	Renal (60), Feces (22)/ Renal (90)	2.5/6.2
Sitagliptin and metformin	87/50 to 60	38/Negligible (% not reported)	Liver, minimal (% not reported)/None	Renal (87), Feces (13)/ Renal (90)	12.4/6.2

V. Drug Interactions

Major drug interactions with the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 5.

Table 5. Major Drug Interactions with the DPP-4 Inhibitors²⁵

Generic Name(s)	Interaction	Mechanism
Linagliptin	Tipranavir	Concurrent use of linagliptin and tipranavir may result in decreased linagliptin exposure.
Saxagliptin	Cobicistat	Concurrent use of cobicistat and saxagliptin may result in increased plasma concentrations of saxagliptin.
Metformin	Iodinated contrast materials, parenteral	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis.
Pioglitazone	Ifosfamide	Concurrent use of ifosfamide and pioglitazone may result in increased neurotoxic and nephrotoxic effects.
Pioglitazone	Tolvaptan	Concurrent use of pioglitazone and tolvaptan may result in decreased tolvaptan plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 6. The boxed warning for DPP-4 inhibitor combination products containing metformin is listed in Table 7 and for alogliptin with pioglitazone in Table 8. There have been postmarketing reports of serious hypersensitivity reactions in patients taking DPP-4 inhibitors. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. There have also been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking DPP-4 inhibitors.¹⁻¹¹

Table 6. Adverse Drug Events (%) Reported with the DPP-4 Inhibitors^{1-11,26}

Adverse Event	Single Entity Agents*				Combination Products*				
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin and Metformin†	Alogliptin and Pioglitazone†	Linagliptin and Metformin†	Saxagliptin and Metformin†	Sitagliptin and Metformin†
Abdominal pain	-	-	1.7 to 2.4	2.3	-	-	-	-	2.2 to 3.0
Arthralgia	-	5.7	-	-	-	-	-	-	-
Back pain	-	6.4	-	-	4.3	4.2	-	-	-
Cough	-	2.7	-	-	-	-	✓	-	-
Decreased appetite	-	-	-	-	-	-	✓	-	-
Diarrhea	-	-	-	3	5.5	-	6.3	5.8 to 9.9	2.4 to 7.5
Fracture	-	-	✓ ‡	-	-	-	-	-	-
Gastroenteritis	-	-	1.9 to 2.3	-	-	-	-	-	-
Headache	4.2	5.7	6.5 to 7.5	1.1 to 5.9	5.3	-	-	7.5	2.7 to 5.9
Hyperlipidemia	-	2.7	-	-	-	-	-	-	-
Hypersensitivity	0.6	✓	1.5	✓	-	-	✓	-	✓
Hypertension	-	-	-	-	5.5	-	-	-	-
Hypertriglyceridemia	-	2.4	-	-	-	-	-	-	-
Hypoglycemia	1.5	7.6 to 22.9	2.7 to 20.0	0.6 to 15.5	1.9 to 5.3	0 to 3.8	1.4 to 22.9	3.4 to 7.8	15.3 to 16.4
Infection	-	-	✓	-	-	-	-	-	-
Lymphopenia	-	-	0.5 to 1.5	-	-	-	-	-	-
Myalgia	-	✓	-	-	-	-	-	-	-
Nasopharyngitis	4.4	4.3	6.9	5.2 to 11.0	6.8	4.9	6.3	6.9	6.1 to 11.0
Nausea	-	-	-	1.4	-	-	✓	-	1.6 to 4.8
Pancreatitis	0.2	✓	✓	✓	-	-	✓	-	-
Peripheral edema	-	-	1.2 to 8.1	8.3	-	-	-	-	8.3
Pruritus	-	-	-	-	-	-	✓	-	-
Rash	-	-	0.2 to 0.3	-	-	-	-	-	-
Sinusitis	-	-	2.6 to 2.9	-	-	-	-	-	-
Thrombocytopenia	-	-	✓	-	-	-	-	-	-
Upper respiratory tract	4.2	-	7.7	4.5 to 15.5	8	4.1	-	-	5.5 to 6.2

Adverse Event	Single Entity Agents*				Combination Products*				
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin and Metformin†	Alogliptin and Pioglitazone†	Linagliptin and Metformin†	Saxagliptin and Metformin†	Sitagliptin and Metformin†
infection									
Urinary tract infection	-	-	6.8	-	4.2	-	-	-	-
Vomiting	-	-	2.2 to 2.3	-	-	-	✓	-	1.1 to 2.2
Weight gain	-	2.3	-	-	-	-	-	-	-

-Event not reported or incidence <1%.

✓ Percent not specified.

*Administered as monotherapy or in combination with other antidiabetic agents.

†Adverse reactions for combination therapy only are reported.

‡ Incidence rate of 1 per 100 patient-years (pooled analysis of 2.5, 5, and 10 mg) compared to placebo (0.6 per 100 patient-years).

Table 7. Boxed Warning for DPP-4 Inhibitor Combination Products Containing Metformin⁵⁻¹⁰

WARNING
<p>WARNING: LACTIC ACIDOSIS</p> <ul style="list-style-type: none"> • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. • If metformin-associated lactic acidosis is suspected, immediately discontinue therapy and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

Table 8. Boxed Warning for Alogliptin and Pioglitazone¹¹

WARNING
<p>WARNING: CONGESTIVE HEART FAILURE</p> <ul style="list-style-type: none"> • Thiazolidinediones, including pioglitazone, which is a component of alogliptin-pioglitazone, cause or exacerbate congestive heart failure in some patients. • After initiation of alogliptin-pioglitazone and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone in alogliptin-pioglitazone must be considered. • Alogliptin-pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of alogliptin-pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated.

VII. Dosing and Administration

The usual dosing regimens for the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 9.

Table 9. Usual Dosing Regimens for the DPP-4 Inhibitors^{1-11,26}

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single-Entity Agents			
Alogliptin	<u>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes:</u> Tablet: 25 mg QD	Safety and efficacy in children have not been established.	Tablet: 6.25 mg 12.5 mg 25 mg
Linagliptin	<u>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes:</u> Tablet: 5 mg QD	Safety and efficacy in children have not been established.	Tablet: 5 mg
Saxagliptin	<u>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes:</u> Tablet: 2.5 or 5 mg QD	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg
Sitagliptin	<u>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2</u>	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	diabetes: Tablet: 100 mg QD		100 mg
Combination Products			
Alogliptin and metformin	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both alogliptin and metformin is appropriate:</u> Tablet: initial, individualized based on the patient's current regimen and administered BID; maximum, 25-2,000 mg/day	Safety and efficacy in children have not been established.	Tablet: 12.5-500 mg 12.5-1,000 mg
Alogliptin and pioglitazone	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and pioglitazone is appropriate:</u> Tablet: initial, individualized based on the patient's current regimen and glycemic control and administered QD; maximum, 25-45 mg/day	Safety and efficacy in children have not been established.	Tablet: 12.5-15 mg 12.5-30 mg 12.5-45 mg 25-15 mg 25-30 mg 25-45 mg
Linagliptin and metformin	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and metformin is appropriate:</u> Extended-release tablet: initial, individualized on the basis of both effectiveness and tolerability; maximum, 5-2,000 mg QD Tablet: initial, individualized on the basis of both effectiveness and tolerability; maximum, 2.5-1,000 mg BID	Safety and efficacy in children have not been established.	Extended-release tablet: 2.5-1,000 mg 5-1,000 mg Tablet: 2.5-500 mg 2.5-850 mg 2.5-1,000 mg
Saxagliptin and metformin	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both saxagliptin and metformin is appropriate:</u> Extended-release tablet: initial, individualized on the basis of the patient's current regimen, effectiveness, and tolerability and administered QD; maximum, 5-2,000 mg/day	Safety and efficacy in children have not been established.	Extended-release tablet: 5-500 mg 2.5-1,000 mg 5-1,000 mg
Sitagliptin and metformin	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both sitagliptin and metformin or metformin extended-release is appropriate:</u> Extended-release tablet: initial, individualized based on the patient's current regimen and administered QD; maximum, 100-2,000 mg/day Tablet: initial, individualized based on the patient's current regimen and administered BID; maximum, 100-2,000 mg/day	Safety and efficacy in children have not been established.	Extended-release tablet: 50-500 mg 50-1,000 mg 100-1,000 mg Tablet: 50-500 mg 50-1,000 mg

BID=twice daily, QD=once daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitors are summarized in Table 10.

Table 10. Comparative Clinical Trials with the DPP-4 Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
DeFronzo et al. ²⁷ (2008) Alogliptin Study 010 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo All patients received counseling on diet and exercise.	DB, MC, PC, RCT Treatment naïve patients 18 to 80 years of age with type 2 diabetes, an HbA _{1c} value 7.0 to 10.0%, a BMI 23 to 45 kg/m ² , exercise for ≥1 month and BP ≤180/110 mm Hg	N=329 26 weeks	Primary: Mean change from baseline in HbA _{1c} at week 26 Secondary: Changes in FPG, hyperglycemic rescue, incidence of marked hyperglycemia, changes in body weight and safety endpoints.	Primary: Mean HbA _{1c} decreased significantly more with 12.5 mg (-0.56%; P<0.001) and 25 mg (-0.59%; P<0.001) alogliptin than with placebo (-0.02%) by week 26. Secondary: FPG reductions were significantly greater with alogliptin 12.5 and 25 mg than with placebo at week 26 (-10.3 and -16.4 vs 11.3 mg/dL, respectively; P<0.001 for both comparisons). The percentage of patients who required hyperglycemic rescue was significantly less with alogliptin 12.5 and 25 mg compared to placebo (9.8 and 7.6 vs 29.7%, respectively; P=0.001 and P<0.001, respectively). Differences between treatment and placebo of most other secondary endpoints, including weight loss, were not significant. Most common adverse events occurred with similar or lower frequency in those given alogliptin vs placebo. However, headache occurred more frequently with alogliptin (6.8 to 7.5%) than with placebo (4.7%).
Rosenstock et al. ²⁸ (2008) <u>Low-dose</u> Saxagliptin 2.5 to 40 mg QD vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics ≥21 to ≤70 years of age with an HbA _{1c} ≥6.8 to ≤9.7%, BMI ≤37 kg/m ² , and a screening fasting or random C-peptide	N=338 12 weeks (saxagliptin 2.5, 5, 10, 20, and 40 mg); 6 weeks (saxagliptin 100 mg)	Primary: Change in baseline HbA _{1c} Secondary: Analyses of each dose vs placebo for decreasing HbA _{1c} , FPG, and PPG at 60 minutes from	Primary: With low-dose saxagliptin, the test for log-linear trend across the treatment groups did not demonstrate a significant dose-response relationship in decreasing HbA _{1c} . Placebo-subtracted adjusted mean changes from baseline to week 12 with saxagliptin ranged from -0.45 to -0.63%, with no apparent significant dose-response relationship (P=0.9888). Secondary: After 12 weeks, HbA _{1c} was significantly decreased with low-dose saxagliptin compared to placebo (all doses P<0.007), with similar and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p><u>High-dose</u> Saxagliptin 100 mg QD</p> <p>vs</p> <p>placebo</p>	<p>>0.5 ng/mL</p>		<p>baseline</p>	<p>clinically meaningful decreases in HbA_{1c} achieved with all doses of saxagliptin. Adjusted mean baseline decreases exceeded 0.70% with each saxagliptin dose compared to 0.27% with placebo. With high-dose saxagliptin, HbA_{1c} was significantly decreased compared to placebo (-1.09 vs -0.36%; P value not reported).</p> <p>With both low- and high-dose saxagliptin, decreases in FPG were evident after two weeks of treatment, and ranged from -11.0 to -22.0 mg/dL with low-dose saxagliptin compared to 3.0 mg/dL with placebo, and -26.3 mg/dL with high-dose saxagliptin compared to -3.3 mg/dL with placebo (P values not reported).</p> <p>With low-dose saxagliptin decreases in PPG at 60 minutes during a liquid meal tolerance test ranged from -24.0 to -41.0 mg/dL compared to -1.0 mg/dL with placebo (P value not reported). With high-dose saxagliptin it was -45.0 mg/dL compared to -17.0 mg/dL with placebo (P value not reported).</p>
<p>Rosenstock et al (abstract).²⁹ (2009)</p> <p><u>Randomized cohort</u> Saxagliptin 2.5 to 10 mg QD</p> <p>vs</p> <p>placebo</p> <p><u>Open-label cohort</u> Saxagliptin 10 mg QD</p> <p>vs</p> <p>placebo</p>	<p>OL, PC, RCT</p> <p>Treatment-naïve type 2 diabetics with inadequate glycemic control, and an HbA_{1c} ≥7.0 and ≤10.0%</p>	<p>N=401 (N=66 in the OL cohort)</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and PPG, proportion of patients achieving an HbA_{1c} <7.0%</p>	<p>Primary: In the main treatment cohort, saxagliptin significantly decreased HbA_{1c} compared to placebo (-0.43, -0.46, and -0.54 vs 0.19% for placebo; all P<0.0001).</p> <p>Secondary: Saxagliptin significantly decreased FPG compared to placebo (-15, -9, and -17 vs 6 mg/dL; P=0.0002, P=0.0074, and P<0.0001).</p> <p>The decrease in PPG AUC with saxagliptin 2.5 (-6,868 [mg/minute]/[dL], 5 (-6,896 [mg/minute]/[dL], and 10 mg (-8,804 [mg/minute]/[dL] compared to placebo (-647 [mg/minute]/[dL] was only significant with saxagliptin 5 (P=0.0002) and 10 mg (P<0.0001).</p> <p>Greater proportions of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (35 [P value not significant], 38 [P=0.0443], and 41 [P=0.0133] vs 24%).</p> <p>Decreases in HbA_{1c}, FPG, and PPG AUC were observed in the OL cohort.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Scircia et al.³⁰ (2013) SAVOR-TIMI</p> <p>Saxagliptin 5 mg QD (2.5 mg daily in patients with an estimated glomerular filtration rate ≤50 mL per minute)</p> <p>vs</p> <p>placebo</p>	<p>RCT</p> <p>Type 2 diabetics ≥40 years of age with an HbA_{1c} ≥6.5 to ≤12% and either a history of established cardiovascular disease or multiple risk factors for vascular disease</p>	<p>N=16,492</p> <p>2.1 years</p>	<p>Primary: A composite of cardiovascular death, myocardial infarction or ischemic stroke</p> <p>Secondary: A composite endpoint (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure), hospitalization rate for heart failure and cases of pancreatitis</p>	<p>Primary: A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3 and 7.2%, respectively; HR, 1.00; 95% CI, 0.89 to 1.12; P=0.99 for superiority; P<0.001 for noninferiority); the results were similar in the “on-treatment” analysis (HR, 1.03; 95% CI, 0.91 to 1.17).</p> <p>Secondary: The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1,059 patients in the saxagliptin group and in 1,034 patients in the placebo group (12.8 and 12.4%, respectively; HR, 1/09; 95% CI, 0.94 to 1.11; P=0.66).</p> <p>More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5 vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; P=0.007).</p> <p>Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1 and 0.1% in the two groups, respectively).</p>
<p>Aschner et al.³¹ (2006)</p> <p>Sitagliptin 100 mg QD</p> <p>vs</p> <p>sitagliptin 200 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Type 2 diabetics 18 to 75 years of age, either receiving or naïve to oral antihyperglycemic agents, and an HbA_{1c} 8.0%</p>	<p>N=741</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, PPG, fasting insulin, proinsulin, fasting lipids, β cell function, and insulin resistance</p> <p>Secondary: Safety and tolerability</p>	<p>Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (100 mg treatment difference, -0.79% [95% CI, -0.96 to -0.62] and 200 mg treatment difference, -0.94% [95% CI, -1.11 to -0.77]); a significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (41 and 45 vs 17%; P<0.001 for both).</p> <p>Sitagliptin significantly decreased FPG compared to placebo (100 mg treatment difference, -17.1 mg/dL and 200 mg treatment difference, -21.3 mg/dL; P<0.001 for both).</p> <p>Sitagliptin significantly reduced two-hour PPG compared to placebo (-48.9 and -56.3 vs -2.2 mg/dL; P<0.001 for both).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>There were no significant effects on fasting insulin and proinsulin with either treatment.</p> <p>Sitagliptin also had no significant effects on fasting lipids.</p> <p>HOMA-B was significantly increased and the proinsulin:insulin ratio was significantly decreased with sitagliptin compared to placebo, indicating improved β cell function ($P \leq 0.001$ and $P \leq 0.01$, respectively).</p> <p>Secondary: There were fewer sitagliptin-treated patients compared to placebo-treated patients that required rescue therapy (8.8 and 4.8 vs 20.6%; $P < 0.001$). No meaningful differences in clinical adverse effects were noted between the two treatments. The incidence of hypoglycemia was similar among the two treatments. Both doses of sitagliptin were well tolerated.</p>
<p>Hanefeld et al.³² (2007)</p> <p>Sitagliptin 25 mg QD vs sitagliptin 50 mg QD vs sitagliptin 50 mg BID vs sitagliptin 100 mg QD vs</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetics 23 to 74 years of age and an HbA_{1c} 7.6 to 7.8%</p>	<p>N=555</p> <p>12 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, mean daily glucose, HOMA-B, QUICKI, and HOMA-IR</p> <p>Secondary: Adverse events, body weight</p>	<p>Primary: Sitagliptin significantly decreased HbA_{1c} by -0.39 to -0.56% compared to placebo ($P < 0.05$).</p> <p>Sitagliptin significantly decreased FPG by -11.0 to -17.2 mg/dL compared to placebo ($P < 0.05$), and the largest decrease was achieved with sitagliptin 100 mg QD.</p> <p>Sitagliptin significantly improved mean daily glucose (-14.0 to -22.6 mg/dL; $P < 0.05$).</p> <p>HOMA-B was significantly increased (11.3 to 15.2; $P < 0.05$) with sitagliptin, whereas there was no significant changes in QUICKI and HOMA-IR with sitagliptin compared to placebo.</p> <p>Secondary: Overall, there was a low frequency of hypoglycemia observed with sitagliptin.</p> <p>There was no change in body weight observed with any treatment.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo</p> <p>Raz et al.³³ (2006)</p> <p>Sitagliptin 100 mg QD</p> <p>vs</p> <p>sitagliptin 200 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetics 18 to 75 years of age with an HbA_{1c} 7.0 to 10.0%</p>	<p>N=521</p> <p>18 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, fasting insulin, proinsulin, and lipids; safety and tolerability</p>	<p>Primary: Sitagliptin (100 mg, -0.60% [95% CI, -0.82 to -0.39] and 200 mg, -0.48% [95% CI, -0.70 to -0.26]) significantly decreased HbA_{1c} compared to placebo (P<0.001).</p> <p>Secondary: Sitagliptin (100 mg, -1.1 mmol/L [95% CI, -1.7 to -0.5] and 200 mg, -0.9 mmol/L [95% CI, -1.5 to -0.3]) significantly decreased FPG compared to placebo (P<0.001).</p> <p>There were no significant effects on fasting insulin, proinsulin, or fasting lipids with either treatment.</p> <p>Rescue therapy was required for 8.8, 11.7, and 17.3% of patients receiving sitagliptin 100 mg, sitagliptin 200 mg, and placebo (P value not reported). Treatment with sitagliptin was well tolerated, and no significant differences between treatments in the incidence of adverse effects were observed. The incidence of hypoglycemia and gastrointestinal side effects was similar between the two treatments.</p>
<p>Nonaka et al.³⁴ (2007)</p> <p>Sitagliptin 100 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Japanese patients with type 2 diabetics, HbA_{1c} ≥6.5 to <10.0%, and FPG ≥126 to ≤240 mg/dL</p>	<p>N=151</p> <p>12 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, PPG, body weight; adverse effects</p> <p>Secondary: Not reported</p>	<p>Primary: Sitagliptin (-0.65%; 95% CI, -0.80 to -0.50) significantly decreased HbA_{1c} compared to placebo (0.41%; 95% CI, 0.26 to 0.56; treatment difference, -1.05%; 95% CI, -1.27 to -0.84; P <0.001). A significantly greater proportion of patients receiving sitagliptin achieved HbA_{1c} <7.0% compared to patients receiving placebo (P<0.001).</p> <p>Sitagliptin (-22.5 mg/dL; 95% CI, -28.0 to -17.0) significantly decreased FPG compared to placebo (9.4 mg/dL; 95% CI, 3.9 to 14.9; treatment difference, -31.9 mg/dL; 95% CI, -39.7 to -24.1; P<0.001).</p> <p>Sitagliptin (-69.3 mg/dL; 95% CI, -85.3 to -53.4) significantly decreased PPG compared to placebo (12.0 mg/dL; 95% CI, -6.5 to 30.5; treatment difference, -81.3 mg/dL; 95% CI, -105.8 to -56.9; P<0.001).</p> <p>Body weight was unchanged compared to baseline with sitagliptin (-0.1</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>kg), but significantly (P<0.01) different compared to placebo (-0.7 kg).</p> <p>No notable difference in adverse events, including hypoglycemia, was observed between the two treatments.</p> <p>Secondary: Not reported</p>
<p>Hartley et al.³⁵ (2015)</p> <p>Sitagliptin vs glimepiride</p>	<p>DB, MC, NI, RCT</p> <p>Patients ≥65 and ≤85 years of age with type 2 diabetes that was inadequately controlled with diet and exercise alone</p>	<p>N=480</p> <p>30 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, and body weight; incidence of symptomatic hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: After 30 weeks, the least squares (LS) mean change in HbA_{1c} baseline was -0.32% with sitagliptin and -0.51% with glimepiride, for a between-group difference of 0.19% (95% CI, 0.03 to 0.34). This result met the pre-specified criterion for declaring non-inferiority. The LS mean change in FPG from baseline was -14.5 mg/dL with sitagliptin and -21.2 mg/dL with glimepiride, for a between-group difference of 6.7 mg/dL (95% CI, 0.7 to 12.7). The percentages of patients with adverse events of symptomatic hypoglycemia were 0.8% in the sitagliptin group and 4.7% in the glimepiride group (between-treatment difference, -3.9 %; P=0.009). The LS mean change in body weight from baseline was 0.4 kg with sitagliptin and 1.1 kg with glimepiride, for a between-group difference of -0.7 kg (P=0.011).</p> <p>Secondary: Not reported</p>
<p>Scott et al.³⁶ (2007)</p> <p>Sitagliptin 5 mg BID vs sitagliptin 12.5 mg BID vs sitagliptin 25 mg</p>	<p>AC, DB, PC, RCT</p> <p>Type 2 diabetics 21 to 75 years of age, inadequately controlled (HbA_{1c} 7.9%) with diet and exercise</p>	<p>N=743</p> <p>12 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, mean daily glucose, and body weight; adverse effects</p> <p>Secondary: Not reported</p>	<p>Primary: Sitagliptin (-0.38 to -0.77%) significantly decreased HbA_{1c} compared to placebo (P<0.001). Sitagliptin 50 mg achieved the greatest decrease. The placebo subtracted difference in HbA_{1c} of glipizide was -1.00%.</p> <p>Sitagliptin significantly decreased FPG and mean daily glucose compared to placebo (P values not reported).</p> <p>There was no difference between sitagliptin and placebo with changes in body weight. Glipizide resulted in a modest weight gain compared to placebo (P value not reported).</p> <p>The incidence of hypoglycemia was highest with glipizide (17%) compared to placebo (2%) and sitagliptin (0 to 4%, not dose-dependent).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs sitagliptin 50 mg BID vs glipizide 5 to 20 mg daily vs placebo				Secondary: Not reported
Chan et al. ³⁷ (2008) <u>Phase I</u> Sitagliptin 25 to 50 mg QD vs placebo <u>Phase II</u> Sitagliptin 25 to 50 mg daily and placebo vs glipizide 2.5 to 20 mg daily and placebo	DB, PC, PG, RCT Patients ≥18 years of age with type 2 diabetes, baseline HbA _{1c} of 6.5 to 10.0%, and renal insufficiency	N=91 54 weeks (Phase I was 12 weeks; Phase II was 42 weeks)	Primary: Safety and tolerability Secondary: Efficacy	Primary: Adverse events were similar among patients receiving sitagliptin and placebo/glipizide, including serious adverse events (30.8 and 38.5%, respectively), drug-related serious adverse events (1.5 and 0.0%, respectively), and adverse events leading to discontinuation. Incidences of adverse events by body systems and specific clinical adverse events were also similar between the sitagliptin and placebo/glipizide groups, with the exception of hypoglycemia and anemia. Hypoglycemia occurred in 4.6% of patients receiving sitagliptin and 23.1% of patients receiving placebo/glipizide. Anemia occurred in 3.1% of patients receiving sitagliptin and 15.4% of patients receiving placebo/glipizide. There was a higher incidence of MI (4.6 and 0.0%) and heart failure (7.7 and 3.8%) in the sitagliptin group compared to the placebo/glipizide group, respectively. The number of patients experiencing cardiovascular events per 100 patient-years was similar between groups. There were six deaths (7.7%) in the sitagliptin group and one death (3.8%) in the placebo/glipizide group. This represents an overall mortality rate of 7.3 deaths per 100 patient-years, with 8.8 and 4.0 deaths per 100 patient-years in the sitagliptin and placebo/glipizide groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>No clinically meaningful differences were observed for laboratory safety measures, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine phosphokinase, uric acid, electrolytes, white blood cell count or absolute neutrophil count between groups.</p> <p>At week 54, the mean change from baseline in serum creatinine for patients with moderate renal insufficiency was -0.02 and 0.69 mg/dL in the sitagliptin and placebo/glipizide groups, respectively.</p> <p>At week 54, small (2 mm Hg) mean decreases in systolic, diastolic and mean arterial BPs were observed for patients on sitagliptin compared to those on placebo/glipizide.</p> <p>At week 54, there was a small mean decrease in body weight from baseline in the sitagliptin group (-0.9 kg) compared with no mean change in the placebo/glipizide group (0.0 kg).</p> <p>Secondary: At week 12, the mean change from baseline in HbA_{1c} was -0.6% (95% CI, -0.8 to -0.4%) in the sitagliptin group compared with -0.2% (95% CI, -0.4 to 0.1%) in the placebo group</p> <p>At week 12, the mean change from baseline in FPG was -25.5 mg/dL (95% CI, -38.2 to -12.8 mg/dL) with sitagliptin and -3.0 mg/dl (95% CI, -15.7 to 9.6) with placebo.</p> <p>At week 54, the mean and least squares mean change from baseline in HbA_{1c} with sitagliptin was -0.7% in the prespecified analysis and in the ANCOVA analysis. The mean and least squares mean changes from baseline were -1.0 and -0.8%, respectively in the placebo/glipizide group. Between-group testing for efficacy was not performed at the week 54 time point.</p> <p>At week 54, the mean percent changes in lipids were as follows for sitagliptin: TC (+4.3%; 95% CI, -1.5 to 10.1), LDL-C (+11.9%; 95% CI, 1.6 to 22.2), and non-HDL-C (+7.1%; -1.2 to 15.3), TGs (-0.7%; 95% CI,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>-13 to 11.5), and HDL-C (+0.9%; 95% CI, -5.9 to 7.7). The mean percent changes in lipids in the placebo/glipizide group were as follows: TC (-0.2%; 95% CI, -10.5 to 10.0), LDL-C (3.3%; 95% CI, -8.6 to 15.2), non-HDL-C (-1.6%; 95% CI, -13.7 to 10.5), TG (+0.9%; 95% CI, -27.5 to 29.3), and HDL-C (+6.6%; 95% CI, -5 to 18.2).</p>
<p>DeFronzo et al.³⁸ (2008)</p> <p>Sitagliptin 100 mg QD for 2 weeks</p> <p>vs</p> <p>exenatide 5 µg SC BID for 1 week, then 10 µg SC BID for 1 week</p>	<p>DB, MC, RCT, XO</p> <p>Patients 18 to 70 years of age with type 2 diabetes who were treated with a stable regimen of metformin, HbA_{1c} 7.0 to 11.0%, FPG <280 mg/dL, and BMI 25 to 45 kg/m²</p>	<p>N=95</p> <p>4 weeks</p>	<p>Primary: 2-hour PPG</p> <p>Secondary: Postprandial insulin, glucagon, active GLP-1 and TG concentrations, and safety</p>	<p>Primary: The 2-hour PPG concentration (least square mean) was lower for exenatide compared to sitagliptin (133 vs 208 mg/dL; P<0.0001). In the intent-to-treat population, the 2-hour PPG concentration was lower with exenatide compared to sitagliptin (166 vs 210 mg/dL, respectively; P<0.0001).</p> <p>The change in 2-hour PPG concentration (least square mean) from baseline was -112 mg/dL for exenatide compared to -37 mg/dL for sitagliptin (P<0.0001).</p> <p>FPG was similar following treatment with exenatide (-15 mg/dL) and sitagliptin (-19 mg/dL; P=0.3234).</p> <p>Following crossover to the alternate therapy, patients switched from exenatide to sitagliptin experienced an increase in mean 2-hour PPG +73 mg/dL. Patients switched from sitagliptin to exenatide treatment experienced a reduction in the mean 2-hour PPG concentration -76 mg/dL.</p> <p>Secondary: The acute insulin response was greater for exenatide compared to sitagliptin (P=0.0017).</p> <p>Both exenatide and sitagliptin reduced the mean postprandial plasma glucagon concentration compared to baseline; however, the reduction was greater with exenatide compared to sitagliptin (P=0.0011).</p> <p>Both exenatide and sitagliptin both reduced mean postprandial TG concentrations compared to baseline; however, the decrease was greater with exenatide compared to sitagliptin (P=0.0118).</p> <p>Exenatide reduced the rate of gastric emptying compared to baseline and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>to sitagliptin (P<0.0001). Sitagliptin had no effect on gastric emptying).</p> <p>Adverse events with exenatide and sitagliptin were mild-to-moderate. The most common adverse events were gastrointestinal with both treatments. Nausea was experienced by 34% of patients treated with exenatide and 12% of patients treated with sitagliptin. Vomiting was experienced by 24% of patients treated with exenatide and 3% of patients treated with sitagliptin. No serious treatment-emergent adverse events were reported during the study.</p>
<p>Aschner et al.³⁹(2010)</p> <p>Sitagliptin 100 mg QD</p> <p>vs</p> <p>metformin 1,000 mg BID</p>	<p>AC, DB, RCT</p> <p>Patients 18 to 78 years of age with type 2 diabetes mellitus who were treatment naïve with an HbA_{1c} 6.5 to 9.0%</p>	<p>N=1,050</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Proportions of patients with HbA_{1c} <7.0% or <6.5%, change in FPG, fasting serum insulin, fasting serum proinsulin, and lipid parameters</p>	<p>Primary: In the per protocol population, the change in HbA_{1c} (least square mean) from baseline at week 24 was -0.43% in the sitagliptin group and -0.57% in the metformin group (difference, 0.14%; 95% CI, 0.06 to 0.21), which demonstrated the non-inferiority of sitagliptin to metformin.</p> <p>In the full analysis set, the HbA_{1c} change from baseline at week 24 was -0.38% (95% CI, -0.43 to -0.32) in the sitagliptin group and -0.55% (95% CI, -0.61 to -0.50) in the metformin group (difference, 0.18%; 95% CI, 0.10 to 0.25), which demonstrated the non-inferiority of sitagliptin to metformin.</p> <p>Secondary: The proportion of patients with an HbA_{1c} <7.0% at week 24 was greater with metformin (76%) compared with sitagliptin (69%; difference, -7.1%; 95% CI, -12.9 to -1.2).</p> <p>The proportion of patients with an HbA_{1c} <6.5% was not statistically different between the metformin (39%) and sitagliptin (34%) groups (difference, -5.6%; 95% CI, -11.8 to 0.8).</p> <p>The change from baseline in FPG was greater with metformin (-19.4 mg/dl compared with sitagliptin (-11.5 mg/dL).</p> <p>The reduction in fasting proinsulin was greater in the metformin group, which resulted in a larger reduction in the proinsulin/insulin ratio at week 24.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Both treatments produced similar increases in β-cell function and reductions in insulin resistance over 24 weeks.</p> <p>HDL-C was improved with both treatments. TGs were slightly reduced with sitagliptin. Small increases in TC were observed for each group, with a slightly greater increase for sitagliptin. Modest increases in LDL-C and non-HDL-C were observed with sitagliptin, but not metformin over 24 weeks.</p> <p>The incidence of drug-related adverse events was lower in the sitagliptin group than in the metformin group. The incidence of gastrointestinal adverse events overall was lower in the sitagliptin group compared with the metformin group (11.6 vs 20.7%, respectively). Hypoglycemia occurred at a low rate in both groups (1.7% with sitagliptin and 3.3% with metformin; P=0.116). Body weight was reduced from baseline in both the sitagliptin (-0.6 kg) and metformin (-1.9 kg; P<0.001).</p>
<p>Russell-Jones et al.⁴⁰ (2012) DRUATION-4 Exenatide ER 2 mg SC once weekly vs metformin 2,000 mg/day vs pioglitazone 45 mg/day vs</p>	<p>DB, DD, MC, PG, RCT Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m², and stable weight</p>	<p>N=820 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported QOL</p>	<p>Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively.</p> <p>Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001).</p> <p>Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sitagliptin 100 mg/day				<p>Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments.</p> <p>Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks ($P \leq 0.003$ for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; $P=0.892$).</p> <p>No clinically significant changes in serum lipids were observed with any treatment.</p> <p>Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin ($P < 0.001$ for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER ($P < 0.001$ for both), and the change with exenatide ER was similar to sitagliptin ($P=0.329$).</p> <p>Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment.</p> <p>All treatments resulted in improvements in perceived treatment</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Monami et al.⁴¹ (2011)</p> <p>DPP-4 inhibitors (linagliptin, alogliptin*, sitagliptin, saxagliptin, vildagliptin*)</p> <p>vs</p> <p>placebo or active comparator (oral hypoglycemic agents and/or insulin)</p>	<p>MA (53 trials)</p> <p>Patients with type 2 diabetes who were receiving a DPP-4 inhibitor</p>	<p>N=33,881</p> <p>≥24 weeks</p>	<p>Primary: Incidence of cancer</p> <p>Secondary: Incidence of pancreatitis, all-cause and cardiovascular mortality, incidence of major cardiovascular events</p>	<p>satisfaction, weight-related QOL, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported).</p> <p>Primary: There were 176 cases of cancer (107 and 69 in patients receiving DPP-4 inhibitors and comparators, respectively); 12.5% were gastrointestinal, 5.7% were pancreatic, 6.2% were pulmonary, 14.7% were mammary gland/female genital tract, 11.3% were male urogenital tract, 3.4% were thyroid, and 26.1% were of another origin. There was no difference in the proportion of cases between patients receiving DPP-4 inhibitors or a comparator (P=0.90).</p> <p>Secondary: The risk of pancreatitis with DPP-4 inhibitors was 0.786 (P=0.55).</p> <p>The number of reported deaths was 28 and 31 with DPP-4 inhibitors and comparators, respectively. Cardiovascular deaths occurred in 10 patients receiving DPP-4 inhibitors and 20 patients receiving comparators. The risk for all-cause death and cardiovascular death in patients receiving DPP-4 inhibitors was 0.668 (P=0.149 and P=0.054, respectively).</p> <p>There were 137 and 120 major cardiovascular events reported with DPP-4 inhibitors and comparators, respectively. DPP-4 inhibitors were associated with a significantly lower risk of major cardiovascular events (OR, 0.689; P=0.006).</p>
<p>Fakhoury et al.⁴² (2010)</p> <p>Incretin-based therapies (exenatide, liraglutide, vildagliptin*, and sitagliptin)</p>	<p>MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, vildagliptin)</p> <p>Type 2 diabetics ≥18 years of age</p>	<p>N=Not reported</p> <p>Duration varied (4 to 52 weeks)</p>	<p>Primary: Change in baseline HbA_{1c} and weight, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; P<0.001) significantly decrease HbA_{1c} compared to placebo.</p> <p>Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; P<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; P<0.0010) significantly decreased baseline HbA_{1c}. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				<p>0.95 to -0.73; P<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant.</p> <p>There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; P<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; P<0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; P=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide.</p> <p>Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.56; 95% CI, 1.23 to 5.33; P=0.01). When adjusted for covariates, age was the only variable found to be significant (RR, 1.84; 95% CI, 1.02 to 3.34; P=0.044). Exenatide-treated patients were 140% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.40; 95% CI, 1.39 to 4.11; P=0.002). Liraglutide-treated patients were 69% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 1.69; 95% CI, 1.00 to 2.86; P=0.050).</p> <p>Secondary: Not reported</p>
<p>Amori et al.⁴³ (2007)</p> <p>Incretin therapy (exenatide, liraglutide, sitagliptin and vildagliptin*)</p> <p>vs</p> <p>non-incretin-based therapy (placebo or hypoglycemic agent)</p>	<p>MA (29 RCTs)</p> <p>Type 2 diabetics</p>	<p>N=12,996</p> <p>Duration varied (12 to 52 weeks)</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, proportion of patients achieving an HbA_{1c}<7.0%</p>	<p>Primary: Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA_{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81).</p> <p>Specifically, no difference in the HbA_{1c} was found in OL, non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA_{1c} efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported).</p> <p>Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Exenatide-treated patients were more likely to achieve an HbA_{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in NI trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.</p>
<p>Shyangdan et al.⁴⁴ (2011)</p> <p>GLP-1 receptor agonist based therapies (albiglutide, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)</p> <p>vs</p> <p>non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)</p>	<p>MA (RCTs)</p> <p>Type 2 diabetics ≥18 years of age</p>	<p>N=not reported</p> <p>8 to 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change</p> <p>Secondary: Health-related QOL, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).</p> <p>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78).</p> <p>Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c}</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>(-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported).</p> <p>Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).</p> <p>Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).</p> <p>Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92).</p> <p>Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).</p> <p>Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).</p> <p>Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).</p> <p>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).</p> <p>Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).</p> <p>Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).</p> <p>Secondary: Data on mortality and morbidity were not reported for any treatment.</p> <p>QOL</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Exenatide ER significantly improved weight-related quality of life and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related quality of life and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.</p> <p>Data for liraglutide were not reported.</p> <p>Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).</p> <p>Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.</p> <p>BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported.</p> <p>Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported.</p> <p>FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).</p> <p>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported).</p> <p>PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).</p> <p>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>highly variable.</p> <p>Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.</p> <p>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported.</p> <p>β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.</p>
<p>Pinelli et al.⁴⁵ (2011)</p> <p>GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*)</p> <p>vs</p> <p>exenatide and</p>	<p>MA, SR (5 RCTs)</p> <p>Adult type 2 diabetics</p>	<p>N=not reported</p> <p>Duration varied (not reported)</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, PPG, weight, BP, and lipid profile; safety</p> <p>Secondary: Not reported</p>	<p>Primary: Pooled analysis demonstrates modest decreases in HbA_{1c} favoring long-acting GLP-1 receptor agonists over exenatide (WMD, -0.47%; 95% CI, -0.69 to -0.25) and sitagliptin (WMD, -0.60%; 95% CI, -0.75 to -0.45). Long-acting GLP-1 receptor agonists were significantly more likely to achieve HbA_{1c} <7.0% compared to exenatide (OR, 2.14; 95% CI, 1.38 to 3.34) and sitagliptin (OR, 3.84; 95% CI, 2.78 to 5.31).</p> <p>Pooled analysis demonstrates significant decreases in FPG favored long-acting GLP-1 receptor agonists compared to exenatide (WMD, -18.39 mg/dL; 95% CI, -24.67 to -12.10) and sitagliptin (WMD, -20.96; 95% CI, -27.88 to -14.04).</p> <p>In one trial, exenatide achieved significantly greater decreases in PPG compared to exenatide ER (-124 vs -95 mg/dL; P=0.01). In another trial, exenatide achieved significantly greater decreases in PPG after breakfast</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sitagliptin				<p>(treatment difference, -24 mg/dL; P<0.0001) and dinner (-18 mg/dL; P=0.0005) compared to liraglutide. There was no difference between treatments after lunch. In a third trial, exenatide ER significantly decreased PPG after each meal compared to sitagliptin (P<0.05).</p> <p>Pooled analysis demonstrates significant decreases in weight with long-acting GLP-1 receptor agonists compared to sitagliptin (WMD, -1.99 kg; 95% CI, -2.69 to -1.09), but not exenatide (WMD, -0.48 kg; 95% CI, -1.11 to 0.44).</p> <p>In one trial, exenatide ER significantly decreased SBP compared to sitagliptin (treatment difference, -4 mm Hg; P=0.006), but results were not significant in the three other trials (P values not reported). One trial demonstrated sitagliptin significantly decreased DBP compared to liraglutide (-1.78 vs 0.07 mm Hg; P=0.02). Between-group differences were not significant in the other three trials (P values not reported).</p> <p>Long-acting GLP-1 receptor agonists significantly improved TC compared to other incretin-based therapy in two of four trials. Exenatide ER significantly decreased TC (-12.0 vs -3.9 mg/dL; P value not reported) and LDL-C (-5.0 vs 1.2 mg/dL) compared to exenatide. Liraglutide significantly decreased TC compared to sitagliptin (-6.60 vs -0.77 mg/dL; P=0.03). In one trial, long-acting GLP-1 receptor agonists significantly improved TG compared to incretin-based therapy (-36 with liraglutide vs -20 mg/dL with exenatide ER; P=0.05).</p> <p>No episodes of severe hypoglycemia were reported in four of the trials. In another trial, two patients receiving exenatide experienced severe hypoglycemia. Non-severe hypoglycemia occurred infrequently and in similar amounts among the treatments. The most commonly reported adverse events with long-acting GLP-1 receptor agonists were gastrointestinal-related. Compared to exenatide, the incidence of vomiting was significantly decreased with long-acting GLP-1 receptor agonists (OR, 0.55; 95% CI, 0.34 to 0.89), there was a trend towards decreased nausea (OR, 0.58; 95% CI, 0.32 to 1.06), and no difference in diarrhea (OR, 1.03; 95% CI, 0.67 to 1.58). Nausea (OR, 4.70; 95% CI, 1.81 to 12.24), vomiting (OR, 3.22; 95% CI, 1.63 to 6.36), and diarrhea (OR,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>2.32; 95% CI, 1.42 to 3.81) with long-acting GLP-1 receptor agonists were increased compared to sitagliptin. Compared to exenatide, exenatide ER caused more injection site pruritus in two trials (17.6 vs 1.4%), in another trial exenatide had a similar rate of injection site reactions compared to placebo injection (10 vs 7%). Acute pancreatitis was not reported in any trial. One patient receiving liraglutide experienced mild pancreatitis after 88 days of treatment.</p> <p>Secondary: Not reported</p>
Type 2 Diabetes – Combination Therapy				
<p>Nauck et al.⁴⁶ (2009) Alogliptin Study 008</p> <p>Alogliptin 12.5 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD</p> <p>vs</p> <p>placebo</p> <p>All patients were stabilized on metformin and continued this agent throughout treatment at a dose $\geq 1,500$ mg/day or the highest tolerated daily</p>	<p>DB, PC, RCT</p> <p>Treatment naïve patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10% (despite a stable metformin regimen ≥ 3 months in duration), a BMI 23 to 45 kg/m², C-peptide concentration ≥ 0.26 nmol/L and SCR < 1.5 mg/dL (men) or < 1.4 mg/dL (women)</p>	<p>N=527</p> <p>26 weeks</p>	<p>Primary: Mean change from baseline in HbA_{1c} at week 26</p> <p>Secondary: HbA_{1c} and FPG changes from baseline at each study visit, incidence of marked hyperglycemia, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin/insulin ratio, achievement of glycemic goals, changes in body weight and safety evaluations</p>	<p>Primary: The 25 mg combination arm compared to metformin monotherapy resulted in statistically significant improvements from baseline in HbA_{1c} (-0.6 vs -0.1%, respectively; P<0.001). Similar results were found with the 12.5 mg combination arm (P<0.001).</p> <p>Secondary: The 25 mg combination arm compared to metformin monotherapy resulted in statistically significant improvements from baseline in FPG (-17 vs 0 mg/dL, respectively; P<0.01). In addition, comparisons at all time points for measures of HbA_{1c} and FPG favored the combination arms.</p> <p>Fewer patients in the alogliptin treatment groups experienced marked hyperglycemia compared to the placebo group at each time point and the difference in overall incidence was statistically significant for both the 12.5 mg (P<0.001) and 25 mg (P=0.003). In addition, the incidence of hyperglycemic rescue was significantly lower (P\leq0.004) for patients in the alogliptin treatment groups compared to the placebo group.</p> <p>There were no statistically significant differences between the alogliptin groups and placebo changes from baseline to week 26 in fasting plasma proinsulin and insulin levels.</p> <p>Relative to patients in the placebo group, a significantly greater percentage of patients in both the alogliptin 12.5 and 25 mg groups achieved HbA_{1c} levels of $\leq 7.0\%$ (P<0.001) and $\leq 6.5\%$ (P<0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose.				Adverse events were similar across all treatment arms. In addition, the incidence of hypoglycemia was low in all treatment groups; there were no severe hypoglycemic events and no clinically significant hypoglycemic episodes reported.
Pratley et al. ⁴⁷ (2009) Alogliptin Study 009 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo Concomitant therapy with metformin or sulfonylurea at pre-study doses was permitted.	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA _{1c} value 7.5% to 10.0% inadequately controlled on a thiazolidinedione alone or in combination with metformin or a sulfonylurea	N=493 26 weeks	Primary: Mean change from baseline in HbA _{1c} at week 26 Secondary: HbA _{1c} and FPG changes from baseline at each study visit, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin/insulin ratio, HOMA-B, achievement of glycemic goals, changes in body weight and safety evaluations	Primary: The addition of alogliptin 25 mg daily to pioglitazone therapy resulted in significant improvements from baseline compared to placebo in HbA _{1c} (-0.8 vs -0.2%, respectively; P<0.01). Significant improvements from baseline compared to placebo were observed with the 12.5 mg arm. Secondary: The addition of alogliptin 25 mg daily to pioglitazone therapy resulted in significant improvements from baseline compared to placebo FPG (-20 vs -6 mg/dL, respectively; P<0.01). Significant decreases from baseline were observed with the 12.5 mg arm compared to placebo. A significantly larger proportion of patients achieved HbA _{1c} ≤7.0% with alogliptin 12.5 or 25 mg than with placebo (44.2 and 49.2 vs 34.0%, respectively; P≤0.016). The percentage of patients with marked hyperglycemia was significantly lower for alogliptin than placebo (≤25% for both alogliptin groups vs 44.3%, respectively; P<0.001). The incidences of overall adverse events and hypoglycemia were similar across treatment groups, but cardiac events occurred more often with active treatment than placebo.
Pratley et al. ⁴⁸ (2009) Alogliptin Study 007 Alogliptin 12.5 mg QD vs	DB, MC, PC, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA _{1c} value 7.0 to 10.0%, FPG<15.3 mmol/L, BMI 23 to 45 kg/m ² who were	N=500 26 weeks	Primary: Mean change from baseline in HbA _{1c} at week 26 Secondary: Evaluation of the safety of alogliptin and the effects of	Primary: The addition of alogliptin 25 mg to glyburide therapy resulted in statistically significant improvements from baseline in HbA _{1c} at week 26 when compared to placebo (-0.5 vs 0%, respectively; P<0.01). Significant decreases with the 12.5 mg strength compared to placebo were also noted. Secondary: Improvements observed in FPG with alogliptin 12.5 and 25 mg were not statistically significant compared to placebo (-5 and -8 vs 2 mg/dL,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>alogliptin 25 mg QD</p> <p>vs</p> <p>placebo</p> <p>All patients received glyburide at a dose ≥ 10 mg QD.</p>	<p>inadequately controlled on a sulfonylurea for ≥ 3 months</p>		<p>alogliptin on additional measures of glycemic control, β-cell function, plasma lipids, weight and adverse events</p>	<p>respectively; $P > 0.07$).</p> <p>More patients in the alogliptin groups achieved HbA_{1c} levels $\leq 7.0\%$ at week 26 compared to patients in the placebo group. However, only the comparison between alogliptin 25 mg (and not the 12.5 mg strength) and placebo reached statistical significance (34.8 and 29.6 vs 18.2%, respectively; $P = 0.002$ and $P = 0.057$).</p> <p>Fewer patients in the alogliptin (12.5 and 25 mg) groups required hyperglycemia rescue (14.9 and 15.7 vs 28.3%, respectively; $P < 0.05$ for both comparisons).</p> <p>Modest improvements were observed in fasting insulin concentration, proinsulin: insulin ratio and HOMA-b with alogliptin treatment, however these differences were not considered significant. Minor nonsignificant increases in body weight were also observed with alogliptin.</p> <p>Adverse events were similar across all treatment groups. The incidences of hypoglycemia for placebo, alogliptin 12.5 mg and alogliptin 25 mg groups were 11.1, 15.8 and 9.6% respectively.</p>
<p>Rosenstock et al.⁴⁹ (2009)</p> <p>Alogliptin 12.5 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD</p> <p>vs</p> <p>placebo</p> <p>All patients received insulin</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value $\geq 8.0\%$, FPG < 15.3 mmol/L, BMI 23 to 45 kg/m² who were inadequately controlled on insulin at a dose ≥ 15 units and ≤ 100 units per day for at least 8 weeks</p>	<p>N=390</p> <p>26 weeks</p>	<p>Primary: Mean change from baseline in HbA_{1c} at week 26</p> <p>Secondary: Evaluation of the safety of alogliptin and the effects of alogliptin on additional measures of glycemic control, β-cell function, plasma lipids and weight.</p>	<p>Primary: The addition of alogliptin 25 mg once daily to insulin therapy compared to placebo resulted in statistically significant improvements from baseline at week 26 in HbA_{1c} (-0.7 vs -0.1, respectively; $P < 0.05$). Similar decreases were observed with the 12.5 mg strength compared to placebo.</p> <p>Secondary: The addition of alogliptin 25 mg once daily to insulin therapy compared to placebo resulted in statistically significant improvements from baseline at week 26 in FPG (-12 vs 6 mg/dL, respectively; $P < 0.05$). Decreases in FPG and HbA_{1c} compared to placebo with alogliptin were generally observed at all time points.</p> <p>The overall incidences of hyperglycemic rescue were significantly lower in the alogliptin 12.5 and 25 mg groups (21 and 20% respectively) than in the placebo group (40%; $P < 0.001$ for both comparisons).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy with or without metformin.				<p>Differences in other secondary endpoints including change in weight and lipid parameters from baseline did not differ significantly between treatment groups.</p> <p>Incidences of overall adverse events, and of gastrointestinal, dermatological and infection-related events, were similar among groups. There were no differences in the proportions of patients experiencing hypoglycemia among placebo (24%), alogliptin 12.5 mg (27%) and alogliptin 25 mg (27%).</p>
<p>Zannad et al.⁵⁰ (2015) EXAMINE post-hoc analysis</p> <p>Alogliptin vs placebo</p>	<p>DB, MC, RCT</p> <p>Patients with type 2 diabetes receiving antidiabetic therapy (with the exception of a DPP-4 inhibitor or GLP-1 analogue), and had had an acute coronary syndrome event within 15 to 90 days before randomisation</p>	<p>N=5,380</p> <p>Median 533 days</p>	<p>Primary: Composite major adverse cardiac events (MACE) endpoint was cardiovascular death, non-fatal acute myocardial infarction, and non-fatal stroke</p> <p>Secondary: Exploratory extended MACE composite endpoint that combined the first occurrence of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure</p>	<p>Primary: Alogliptin was non-inferior to placebo in lowering the risk of the composite primary endpoint (11.3 vs 11.8%; HR, 0.96; upper boundary of the one-sided 95% CI, 1.16).</p> <p>Secondary: The exploratory extended MACE endpoint was seen in 433 (16.0%) patients assigned to alogliptin and in 441 (16.5%) assigned to placebo (HR, 0.98; 95% CI, 0.86 to 1.12). Hospital admission for heart failure was the first event in 85 (3.1%) patients taking alogliptin compared with 79 (2.9%) taking placebo (HR, 1.07; 95% CI, 0.79 to 1.46). Alogliptin had no effect on composite events of cardiovascular death and hospital admission for heart failure in the post hoc analysis (HR, 1.00; 95% CI, 0.82 to 1.21) and results did not differ by baseline BNP concentration. NT-pro-BNP concentrations decreased significantly and similarly in the two groups.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosenstock et al. ⁵¹ (2013) Alogliptin 25 mg QD vs glipizide 5 mg (titrated to 10 mg if needed)	AC, DB, PRO, RCT Patients aged 65 to 90 years of age with type 2 diabetes on diet and exercise therapy alone during the 2 months prior to screening with HbA _{1c} level of 6.5 to 9.0% or on oral antidiabetic monotherapy with HbA _{1c} of 6.5 to 8.0%	N=441 52 weeks	Primary: HbA _{1c} changes at week 52 from baseline. Secondary: Changes from baseline in HbA _{1c} at all time points, changes in FPG, 2-hour PPG, weight and lipid changes, and adverse events	Primary: Glycemic control with alogliptin was comparable to that with glipizide, with no statistically significant treatment-group differences for any of the corresponding efficacy endpoints. Secondary: Treatment with alogliptin resulted in modest body weight decreases throughout the study, which were significant when compared with the increases observed with glipizide, -0.62 vs 0.60 kg, respectively, by week 52 (P<0.001). Triglycerides also significantly improved with alogliptin (8.0% decrease) compared with glipizide (1.2% increase; P=0.046), whereas no significant differences were noted for total cholesterol (0.4 vs 0.3% decrease), high-density lipoprotein cholesterol (1.7 vs 0.6% increase) or low-density lipoprotein cholesterol (0.8% increase vs 1.3% decrease). Fewer patients discontinued from alogliptin because of adverse events (8.6 vs 12.3% from glipizide).
Del Prato et al. ⁵² (2014) Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs glipizide 5 mg QD, titrated to a maximum of 20 mg	DB, MC, RCT Patients 18 to 80 years of age with type 2 diabetes inadequately controlled on stable-dose metformin	N=2,639 104 weeks	Primary: Mean change from baseline in HbA _{1c} Secondary: Changes over time in HbA _{1c} and FPG, incidence of clinical response (HbA _{1c} ≤6.5 and ≤7.0%), changes in body weight, incidence of hyperglycaemic rescue, and changes in 2-h PPG over time	Primary: From baseline HbA _{1c} values of 7.6% in all three treatment groups, changes up to weeks 52 and 104 showed sustained glycaemic response. In the analysis of mean differences between the treatment groups at week 104, the criteria for non-inferiority to glipizide were satisfied for both alogliptin 12.5 mg (P<0.001) and alogliptin 25 mg (P<0.001), and the criteria for superiority to glipizide were satisfied for alogliptin 25 mg (P=0.010). Secondary: FPG concentration decreased by 0.05 and 0.18 mmol/l for alogliptin 12.5 and 25 mg, respectively, and increased by 0.30 mmol/l for glipizide (P<0.001 for both comparisons with glipizide). Mean weight changes were -0.68, -0.89 and 0.95 kg for alogliptin 12.5 and 25 mg and glipizide, respectively (P<0.001 for both comparisons with glipizide). Hypoglycaemia occurred in 23.2% of patients in the glipizide group vs 2.5 and 1.4% of patients in the alogliptin 12.5 and 25 mg groups, respectively.
Rosenstock et al. ⁵³	DB, PG, RCT	N=655	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2010)</p> <p>Alogliptin 25 mg QD</p> <p>vs</p> <p>alogliptin 12.5 mg QD and pioglitazone 30 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD and pioglitazone 30 mg QD</p> <p>vs</p> <p>pioglitazone 30 mg QD</p>	<p>Treatment naïve patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 11.0%, a BMI 23 to 45 kg/m², who failed diet and exercise interventions for ≥2 months</p>	<p>26 weeks</p>	<p>Mean change from baseline in HbA_{1c} at week 26</p> <p>Secondary: HbA_{1c} and FPG changes from baseline at each study visit, percentage of patients achieving specific HbA_{1c} goals, frequency of glycemic rescue and safety evaluations</p>	<p>Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in HbA_{1c} (-1.7 vs -1.0 and -1.2%, respectively; P<0.01 for both comparisons). Similar reductions were observed with the combination therapy arm involving the 12.5 mg strength.</p> <p>Secondary: Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in FPG (-50 vs -26 and -37 mg/dL, respectively; P<0.01 for both comparisons). In addition, each treatment resulted in prompt and progressive reductions in HbA_{1c} and FPG that were sustained throughout the 26 weeks. In addition, both combination therapy groups were associated with significantly greater percentage of patients meeting glycemic goals compared to monotherapy.</p> <p>Fewer patients in the combination therapy groups required hyperglycemic rescue (3.7 and 2.4% with combination alogliptin 12.5 and 25 mg groups, respectively) than with either pioglitazone (6.1%) or alogliptin monotherapy (11.0%).</p> <p>The safety profile of combination therapy was consistent with that of the individual components. The most frequently reported adverse events included headache, back pain, urinary tract infection and peripheral edema.</p>
<p>DeFronzo et al.⁵⁴ (2012)</p> <p>Alogliptin 12.5 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.5% to 10.0%, FPG <16.7 mmol/L, BMI 23 to 45 kg/m², blood pressure</p>	<p>N=1,554</p> <p>26 weeks</p>	<p>Primary: Mean change from baseline in HbA_{1c} at week 26</p> <p>Secondary: HbA_{1c} and FPG changes from baseline at each study visit, hyperglycemic</p>	<p>Primary: Coadministration of alogliptin and pioglitazone provided significant improvements in HbA_{1c} and FPG compared to placebo, or either treatment as a single agent added to metformin therapy (P<0.01 for all comparisons).</p> <p>Secondary: More patients in the placebo group (41 of 129; 31.8%) required hyperglycemic rescue than in any active treatment group. The alogliptin and pioglitazone therapy groups had a higher percentage of patients requiring hyperglycemic rescue (8.5 to 14.7%) than any combination therapy (1.5 to 4.6%).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pioglitazone 15 mg QD vs pioglitazone 30 mg QD vs pioglitazone 45 mg QD vs alogliptin 12.5 mg QD and pioglitazone 15 mg QD vs alogliptin 12.5 mg QD and pioglitazone 30 mg QD vs alogliptin 12.5 mg QD and pioglitazone 45 mg QD vs	$\leq 160/110$ mm Hg, HGB ≥ 12 g/dL (men) or ≥ 10 g/dL (women), ALT ≤ 2.5 X ULN, TSH \leq ULN, SCR < 133 μ mol/L (men) or < 124 μ mol/L (women), and C-peptide concentration ≥ 0.26 nmol/L who were inadequately controlled on metformin at a dose of $\geq 1,500$ mg/day for ≥ 2 months		rescue, C-peptide, proinsulin, insulin and proinsulin/insulin ratio, HOMA-B, achievement of glycemic goals, changes in body weight and safety evaluations	<p>Measures of β-cell function found a greater decrease in alogliptin 25 mg/pioglitazone compared to pioglitazone alone. However, the decrease in the alogliptin 12.5 mg/pioglitazone arms were similar to the pioglitazone arms alone.</p> <p>Body weight decreased slightly in patients receiving placebo (-0.7 kg) or alogliptin (-0.02 and -0.7 kg for the 12.5 and 25 mg groups, respectively), whereas there were modest but significant increases in body weight in all groups receiving pioglitazone (P values not reported).</p> <p>In general, the combination of alogliptin and pioglitazone was well tolerated. In addition, the incidence of adverse events was similar across treatment groups.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>alogliptin 25 mg QD and pioglitazone 15 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD and pioglitazone 30 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD and pioglitazone 45 mg QD</p> <p>vs</p> <p>placebo</p> <p>Patients received metformin at a dose of 1,500 mg/day.</p>				
<p>Bosi et al.⁵⁵ (2011)</p> <p>Alogliptin 25 mg QD and pioglitazone 30 mg QD</p> <p>vs</p>	<p>AC, DB, MC, PG, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10%, FPG <15.3 mmol/L, BMI 23 to</p>	<p>N=803</p> <p>52 weeks</p>	<p>Primary: Mean change from baseline in HbA_{1c} at weeks 26 and 52</p> <p>Secondary: Mean change from baseline in HbA_{1c}</p>	<p>Primary: In combination with pioglitazone and metformin, alogliptin was associated with a significantly greater decrease compared to the titration of pioglitazone in HbA_{1c} (-0.7 vs -0.3%, respectively; P=0.025) and FPG (-15 vs -4 mg/L, respectively; P<0.001) at 52 weeks. Similar, the decrease was greater with the alogliptin group at 26 weeks (P<0.001).</p> <p>Secondary: In combination with pioglitazone and metformin, alogliptin was associated</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>pioglitazone 45 mg QD</p> <p>All members received metformin at a dose $\geq 1,500$ mg throughout the study.</p>	<p>45 kg/m², blood pressure $\leq 160/110$ mm Hg, and C-peptide concentration ≥ 0.26 nmol/L who were inadequately controlled on metformin at a dose of $\geq 1,500$ mg/day and pioglitazone 30 mg daily for ≥ 2 months</p>		<p>and FPG at all other visits, proportions of patients achieving glycemic goals, proinsulin: insulin ratio, C-peptide, HOMA-B, HOMA insulin resistance, body weight, serum triglycerides, cholesterol, and safety endpoints</p>	<p>with a significantly greater decrease compared to the titration of pioglitazone in FPG (-15 vs -4 mg/L, respectively; $P < 0.001$) at 52 weeks. Decreases favored alogliptin for HbA_{1c} and FPG at 26 weeks and other time points.</p> <p>At week 52, the proportions of patients achieving HbA_{1c} levels ≤ 7.0 (33.2 vs 21.3%, respectively) and $\leq 6.5\%$ (8.7 vs 4.3%, respectively) were significantly higher in the alogliptin group than in the pioglitazone titration group ($P < 0.001$ for all comparisons).</p> <p>Proinsulin: insulin ratio (-0.048 vs -0.007, respectively) and HOMA β-cell function (15.02 vs 2.06, respectively) were significantly improved in the alogliptin group compared to the pioglitazone titration group at 52 weeks ($P < 0.001$ for all comparisons). However, no statistically significant differences in mean change from baseline in C-peptide, HOMA insulin, in body weight, total cholesterol, HDL cholesterol, LDL-C, triglycerides or free fatty acids resistance were observed between the treatment groups at week 52 ($P > 0.05$ for all comparisons).</p> <p>No meaningful differences in incidences of individual adverse events were observed between treatments.</p>
<p>Leiter et al.⁵⁶ (2014)</p> <p>Albiglutide 30 mg once weekly (up-titrated if needed)</p> <p>vs</p> <p>sitagliptin (dosed based on the eGFR value)</p> <p>Patients continued to receive their</p>	<p>DB, MC, RCT</p> <p>Renally impaired patients with type 2 diabetes</p>	<p>N=507</p> <p>52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to 26 weeks</p> <p>Secondary: FPG, weight, achievement of treatment targets, hyperglycemic rescue, and safety.</p>	<p>Primary: The model-adjusted LS mean for the primary end point of change from baseline in HbA_{1c} at week 26 was -0.83% in the albiglutide group and -0.52% in the sitagliptin group, with similar results across all three baseline eGFR groups. The treatment difference (albiglutide vs sitagliptin) was -0.32% (95% CI, -0.49 to -0.15). The upper bound of the CI was below the prespecified noninferiority margin of 0.4%, indicating noninferiority of albiglutide to sitagliptin. A superiority test conducted in accordance with a prespecified, step-wise procedure indicated that albiglutide was statistically superior to sitagliptin ($P = 0.0003$). The treatment effect of albiglutide seen at week 26 was maintained through week 52.</p> <p>Secondary: The change in FPG from baseline at week 26 was -1.42 mmol/L in the albiglutide group and -0.22 mmol/L in the sitagliptin group. At week 26,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>prescribed oral antihyperglycemic medication regimen (metformin, thiazolidinedione, sulfonyleurea, or any combination of these oral antihyperglycemic medications)</p>				<p>the difference in LS means (albiglutide vs sitagliptin) was -1.20 mmol/L ($P<0.0001$). A higher percentage of patients in the albiglutide treatment group achieved the treatment targets of $HbA_{1c} <6.5\%$ and $<7.0\%$ at week 26 (albiglutide 15.3% and 42.6%, respectively, compared with sitagliptin 12.3% and 30.5%, respectively). The treatment difference between albiglutide and sitagliptin was statistically significant ($P=0.0077$) for the treatment target of $HbA_{1c} <7.0\%$ at week 26. There was a statistically significant difference between albiglutide and sitagliptin ($P=0.0017$) in the mean time to hyperglycemia rescue through week 52. The proportion of patients who had required hyperglycemia rescue was lower in the albiglutide group than in the sitagliptin group at week 26 (6.1% [15 patients] vs 12.1% [29 patients]) and at week 52 (17.9% [44 patients] vs. 28.3% [68 patients]). Patients in both treatment groups showed a modest mean loss in body weight through week 26, with a model-adjusted LS mean weight change from baseline of -0.79 kg for albiglutide and -0.19 kg for sitagliptin ($P<0.05$). The incidence of any adverse event and the event rates of on-therapy adverse events over the course of the study were similar between the two treatment groups (83.5% and 347 AEs/100 person-years with albiglutide and 83.3% and 331 AEs/100 person-years with sitagliptin).</p>
<p>Del Prato et al.⁵⁷ (2011) Linagliptin 5 mg/day vs placebo</p>	<p>DB, MC, PC, PG, RCT Type 2 diabetics 18 to 80 years of age with $BMI \leq 40$ kg/m², and either treatment-naïve or had previously received 1 oral antidiabetic agent (excluding TZDs)</p>	<p>N=503 24 weeks</p>	<p>Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an $HbA_{1c} <7.0$ or $<6.5\%$, change in baseline HbA_{1c} by visit over time, proportion of patients with an HbA_{1c} decrease $\geq 0.5\%$, change in baseline FPG, and two-hour PPG,</p>	<p>Primary: Adjusted mean differences of the change in HbA_{1c} significantly favored linagliptin compared to placebo (-0.69%; $P<0.0001$). Secondary: The proportion of patients with a baseline $HbA_{1c} \geq 7.0\%$ who achieved an $HbA_{1c} <7.0\%$ receiving linagliptin and placebo were 25.2 vs 11.6% (OR, 2.9; $P=0.0006$). The difference between linagliptin and placebo in HbA_{1c} decreases from baseline increased over time and favored linagliptin (-0.46% at week six to -0.69% at week 24; $P<0.0001$ for all). The proportion of patients who achieved an HbA_{1c} decrease $\geq 0.5\%$ was 47.1 vs 19.0% with linagliptin and placebo (OR, 4.2; $P<0.0001$). Adjusted mean differences of the decrease in FPG significantly favored</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			safety	<p>linagliptin compared to placebo (-1.3 mmol/L; P<0.0001).</p> <p>Adjusted mean differences of the decrease in two-hour PPG significantly favored linagliptin compared to placebo (-3.2 mmol/L; P<0.0001).</p> <p>Linagliptin was well tolerated. In the total population, 6.6% of patients discontinued treatment prematurely, most frequently due to adverse events (1.8%) or a refusal to continue medication (2.0%). A greater proportion of patients receiving placebo reported at least one adverse event (58.7 vs 52.4%) or serious adverse event (4.2 vs 3.0%). Hyperglycemia was the most frequently reported adverse event (8.6 vs 22.8%). Other more commonly reported adverse events with linagliptin included headache (2.7 vs 1.2%), hypertension (3.6 vs 1.2%), and back pain (2.7 vs 1.8%). No clinically significant findings emerged regarding laboratory analyses or vital signs.</p>
<p>Taskinen et al.⁵⁸ (2011)</p> <p>Linagliptin 5 mg/day vs placebo</p> <p>All patients also received metformin ≥1,500 mg/day.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetics 18 to 80 years of age with BMI ≤40 kg/m², who had inadequate glycemic control on metformin ≥1,500 mg/day (HbA_{1c} 7.0 to 10.0%) or metformin in combination with ≤1 other oral antidiabetic agent (HbA_{1c} 6.5 to 9.0%) for ≥10 weeks prior to trial entry</p>	<p>N=701</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, two-hour PPG, body weight, and β cell function; change in baseline HbA_{1c} and FPG over time; proportion of patients achieving an HbA_{1c} <7.0 and <6.5%; proportion of patients with an HbA_{1c} decrease ≥0.5%; proportion of patients who required rescue medication; safety</p>	<p>Primary: Linagliptin decreased HbA_{1c} by -0.49% compared to 0.15% with placebo (treatment difference, -0.64%; 95% CI, -0.78 to -0.50; P<0.0001).</p> <p>Secondary: Linagliptin significantly decreased FPG compared to placebo (-0.6 vs 0.6 mmol/L; treatment difference, -1.2 mmol/L; P<0.0001).</p> <p>Linagliptin significantly decreased PPG compared to placebo (-2.7 vs 1.0 mmol/L; treatment difference, -3.7 mmol/L; P<0.0001).</p> <p>Neither treatment was associated with a significant change in body weight (-0.4 vs -0.5 kg; P value not reported).</p> <p>HOMA-B demonstrated a clinically relevant difference between treatments in adjusted mean change from baseline at 24 weeks in favor of linagliptin of 11.9 (mU/L)/(mmol/L), for a relative change of 1.26 (mU/L)/(mmol/L) (P=0.0005).</p> <p>The significant difference between the two treatments in decreases in HbA_{1c} increased over time from six to 18 weeks (-0.43 to -0.65%), and then remained stable until trial end (-0.64%). Decreases in FPG over time</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>were similar, with linagliptin-treated patients achieving decreases over time. The difference between the two treatments in terms of adjusted mean change from baseline in FPG increased overtime (-0.9 to -1.2 mmol/L; $P < 0.0001$ for all).</p> <p>Among patients with a baseline $HbA_{1c} \geq 7.0\%$, 26.0 vs 9.0% of those receiving linagliptin and placebo achieved an $HbA_{1c} < 7.0\%$ (OR, 4.4; 95% CI, 2.4 to 8.0; $P = 0.0001$). A significant difference was also observed in achieving $HbA_{1c} < 6.5\%$ for those with a baseline $HbA_{1c} \geq 6.5\%$ (10 vs 2%; OR, 5.5; 95% CI, 1.9 to 15.6; $P = 0.0016$).</p> <p>Fifty and 22% of patients receiving linagliptin and placebo achieved a reduction in $HbA_{1c} \geq 0.5\%$ at 24 weeks (OR, 3.8; 95% CI, 2.5 to 5.7; $P < 0.0001$).</p> <p>More than twice as many patients receiving placebo required rescue medication (19 vs 8%; OR, 0.28; $P = 0.0001$).</p> <p>Overall, linagliptin was well tolerated and adverse events occurred at a similar rate with both treatments. Most adverse events were mild or moderate in intensity. All hypoglycemic events were of mild intensity and assistance was not required by any patient. The incidence of treatment-related adverse events was slightly higher among placebo-treated patients (10.7 vs 6.9%). No clinically significant findings emerged regarding laboratory analyses or vital signs.</p>
<p>Owens et al.⁵⁹ (2011)</p> <p>Linagliptin 5 mg QD</p> <p>vs</p> <p>placebo</p> <p>Patients were also receiving</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetics ≥ 18 to ≤ 80 years of age, BMI ≤ 40 kg/m², and $HbA_{1c} \geq 7.0$ and $\leq 10.0\%$ despite receiving metformin $\geq 1,500$ mg/day and the maximum tolerated</p>	<p>N=1,058</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving an $HbA_{1c} < 6.5$ or $< 7.0\%$; proportion of patients achieving an HbA_{1c} decrease</p>	<p>Primary: Linagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.62%; 95% CI, -0.73 to 0.50; $P < 0.0001$).</p> <p>Secondary: A significantly greater proportion of patients with baseline $HbA_{1c} \geq 7.0\%$ achieved an $HbA_{1c} < 7.0\%$ with linagliptin compared to placebo (29.2 vs 8.1%; $P < 0.0001$).</p> <p>The proportion of patients achieving an HbA_{1c} decrease $\geq 0.5\%$ was 58.2 and 30.2% with linagliptin and placebo (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin and a sulfonylurea.	dose of a sulfonylurea		<p>≥0.5%; change in baseline FPG, fasting plasma insulin, HOMA-B, HOMA-IR, body weight, waist circumference, and lipid profile; use of rescue medication; safety</p>	<p>Linagliptin significantly decreased FPG (treatment difference, -7.0 mmol/L; 95% CI, -1.0 to -0.4; P<0.0001).</p> <p>Linagliptin significantly improved HOMA-B and HOMA-IR compared to placebo (P<0.001).</p> <p>No significant changes in body weight or waist circumference were observed with either treatment.</p> <p>Only placebo-treated patients experienced a meaningful decrease in TG (-12 mg/dL). Changes in TC, HDL-C, and LDL-C were similar between the two treatments.</p> <p>Of the patients receiving linagliptin, 5.4% required rescue medication compared to 13.0% of placebo-treated patients. The likelihood of requiring rescue medication was approximately three times lower with linagliptin (OR, 0.361; P<0.0001).</p> <p>Overall, 66.3 and 59.7% of patients receiving linagliptin and placebo experienced adverse events. The proportion of patients reporting severe adverse events was low with both treatments (2.4 vs 1.5%). Hypoglycemia was the most commonly reported adverse event (22.7 vs 14.8%). Symptomatic hypoglycemia was reported in 16.7 and 10.3% of patients. Hypoglycemia was generally mild or moderate, with severe hypoglycemia reported in 2.7 and 4.8% of patients.</p>
<p>Bajaj et al.⁶⁰ (2014)</p> <p>Linagliptin 5 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Type 2 diabetics ≥18 to ≤80 years of age, BMI ≤45 kg/m², and HbA_{1c} ≥7.5 and ≤10.0% despite receiving metformin ≥1,500 mg/day and pioglitazone 45 mg/day</p>	<p>N=272</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change from baseline in FPG, the percentage of patients who attained HbA_{1c} levels <7.0% and</p>	<p>Primary: Linagliptin significantly reduced HbA_{1c} levels: The placebo-corrected adjusted mean change from baseline at week 24 for linagliptin was -6 mmol/mol; 95% CI, -9 to -3 (-0.57%; 95% CI, -0.83 to -0.31; P<0.0001).</p> <p>Secondary: In patients with baseline HbA_{1c} ≥7.0%, 32.4% of patients in the linagliptin group and 13.8% in the placebo group achieved HbA_{1c} <7.0% (OR, 2.94; P=0.0033). The placebo-corrected adjusted mean change from baseline in FPG at week 24 was -0.57 mmol/l (-10.4 mg/dl; P=0.0280). The incidence of serious adverse events was 2.2% with linagliptin and 3.4%</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<6.5%, the percentage of patients who achieved a reduction of $\geq 0.5\%$ in HbA _{1c}	with placebo. Investigator-defined hypoglycaemia occurred in 5.5% of the linagliptin group and 5.6% of the placebo group. No meaningful changes in mean body weight were noted for either group.
<p>Forst et al.⁶¹ (2010)</p> <p>Linagliptin 1, 5, or 10 mg/day</p> <p>vs</p> <p>placebo</p> <p>vs</p> <p>glimepiride (OL) 1 to 3 mg/day</p> <p>Patients were also receiving metformin.</p>	<p>AC, DB, MC, PC, PG, RCT</p> <p>Type 2 diabetics 21 to 75 years of age with BMI 25 to 40 kg/m², who had inadequate glycemic control on metformin alone (HbA_{1c} 7.5 to 10.0%)</p>	<p>N=333</p> <p>12 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and body weight, proportion of patients achieving an HbA_{1c} $\leq 7.0\%$, proportion of patients with an HbA_{1c} decrease $\geq 0.5\%$, safety</p>	<p>Primary: Placebo corrected decreases in HbA_{1c} were -0.40 ± 0.14 (P=0.006), -4.40 ± 0.14 (P<0.001), and $-8.00 \pm 1.50\%$ (P<0.001) with linagliptin 1, 5, and 10 mg, respectively. Treatment with glimepiride significantly decreased HbA_{1c} compared to treatment with placebo -0.68% (P<0.0001).</p> <p>Secondary: Decreases in FPG were significantly greater with all doses of linagliptin compared to placebo. The placebo corrected FPG decrease were -1.1 (P=0.0020), -1.9 (P<0.0001), and -1.6 mmol/L (P<0.0001) with linagliptin 1, 5, and 10 mg, respectively.</p> <p>After 12 weeks a small decrease in body weight was observed with all doses of linagliptin (-0.15, -0.57, and -1.27 kg, respectively; P values not reported).</p> <p>Only one (1.4%) patient receiving placebo achieved an HbA_{1c} $\leq 7.0\%$ compared to ten (approximately 15%), nine (approximately 15%), and 14 (21%) patients receiving linagliptin 1, 5, and 10 mg/day, respectively (P values not reported).</p> <p>A greater proportion of patients receiving linagliptin achieved an HbA_{1c} decrease $\geq 0.5\%$ compared to patients receiving placebo (43.8 to 53.2 vs 12.9%; P value not reported). In addition, HbA_{1c} decreased by $\geq 1.0\%$ in 14.1, 27.4, 22.7, and 7.7% with linagliptin 1 mg, linagliptin 5 mg, linagliptin 10 mg, and placebo (P values not reported).</p> <p>Linagliptin was well tolerated. The most commonly reported adverse events were considered to be of mild or moderate intensity; however, ten patients experienced severe adverse events. No episodes of hypoglycemia were reported. Three (4.6%) patients experienced hypoglycemia after</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Haak et al.⁶² (2012)</p> <p>Linagliptin 5 mg QD</p> <p>vs</p> <p>metformin 500 mg BID</p> <p>vs</p> <p>metformin 1,000 mg BID</p> <p>vs</p> <p>linagliptin 2.5 mg BID and metformin 500 mg BID</p> <p>vs</p> <p>linagliptin 2.5 mg BID and metformin 1,000 mg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve (HbA_{1c} 7.5 to 11.0%) or who had received one other oral antidiabetic drug (HbA_{1c} 7.0 to 10.5%)</p>	<p>N=791</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1c} at week 24</p> <p>Secondary: Change from baseline in FPG, change from baseline in HbA_{1c} and FPG over time, proportion of patients requiring rescue therapy after failing to achieve pre-specified glycemic targets or discontinuing because of lack of efficacy, safety</p>	<p>dosing with glimepiride.</p> <p>Primary: After 24 weeks, the mean change in HbA_{1c} was 0.1% with placebo, -0.5% with linagliptin 5 mg QD, -0.6% with metformin 500 mg BID, -1.1% with metformin 1,000 mg BID, -1.2% with linagliptin plus metformin 500 mg, and -1.6% with linagliptin plus metformin 1,000 mg.</p> <p>The adjusted placebo-corrected mean changes in HbA_{1c} were -1.7% (95% CI, -2.0 to -1.4) for linagliptin plus metformin 1,000 mg; -1.3% (95% CI, -1.6 to -1.1) for linagliptin plus metformin 500 mg; -1.2% (95% CI, -1.5 to -0.9) for metformin 1,000 mg; -0.8% (95% CI, -1.0 to -0.5) for metformin 500 mg, and -0.6% (95% CI, -0.9 to -0.3) for linagliptin monotherapy (P<0.0001 for all).</p> <p>The mean treatment differences for linagliptin plus metformin 1,000 mg vs metformin and linagliptin monotherapy were -0.5% (95% CI, -0.7 to -0.3) and -1.1% (95% CI, -1.4 to -0.9), respectively. For linagliptin plus metformin 500 mg, the respective mean differences were -0.6% (95% CI, -0.8 to -0.4) and -0.8% (95% CI, -1.0 to -0.6; P<0.0001 for all).</p> <p>Secondary: The adjusted placebo-corrected mean changes in FPG from baseline were -3.3 mmol/L (95% CI, -4.0 to -2.6) and -2.4 mmol/L (95% CI, -3.1 to -1.7) in the linagliptin plus metformin 1,000 mg and linagliptin plus metformin 500 mg groups, respectively. This is compared to -2.3 mmol/L (95% CI, -3.0 to -1.7), -1.4 mmol/L (95% CI, -2.1 to -0.8) and -1.0 mmol/L (95% CI, -1.7 to -0.3) in the metformin 1,000 mg, metformin 500 mg, and linagliptin monotherapy groups, respectively (P<0.0001 for all).</p> <p>The proportion of patients requiring rescue therapy for inadequate glycemic control at week 24 was lower in the combination therapy groups (linagliptin plus metformin 1,000 mg, 4.3%; linagliptin plus metformin 500 mg, 7.3%) compared to either monotherapy alone (metformin 1,000 mg, 8.0%; metformin 500 mg, 13.5%; linagliptin, 11.1%).</p> <p>The proportion of patients reporting adverse events were comparable across the active treatment groups.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Haak et al.⁶³ (2013)</p> <p>linagliptin 2.5 mg plus metformin 500 mg (both twice daily)</p> <p>vs</p> <p>linagliptin 2.5 mg plus metformin 1000 mg (both twice daily)</p> <p>vs</p> <p>metformin 1000 mg twice daily monotherapy</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve (HbA_{1c} 7.5 to 11.0%) or who had received one other oral antidiabetic drug (HbA_{1c} 7.0 to 10.5%)</p> <p>(extension study of Haak et al.⁵²)</p>	<p>N=566</p> <p>54 weeks</p>	<p>Primary: Safety</p> <p>Secondary: Change from baseline in HbA_{1c} and FPG, the percentages of patients who achieved target HbA_{1c} levels of < 7.0 or < 6.5%, the percentages of patients with a reduction in HbA_{1c} levels of ≥ 0.5%, and use of rescue therapy</p>	<p>Primary: The incidences of treatment-emergent AEs during the extension period were comparable across the groups, ranging between 66 and 77%. Most adverse events were of mild or moderate intensity, with the majority considered unrelated to study drug.</p> <p>Secondary: All three groups maintained the reduction in HbA_{1c} achieved at the end of the six-month trial, with changes of 0.12 ± 0.72%, 0.08 ± 0.74% and 0.13 ± 0.54%, for the metformin 1000 group, linagliptin 2.5 + metformin 500, and linagliptin 2.5 + metformin 1000 groups, respectively.</p> <p>The overall incidence of rescue medication use was lower in the linagliptin 2.5 + metformin 1000 treatment group (14.0%) than in the linagliptin 2.5 + metformin 500 (27.6%) and metformin 1000 (24.7%) treatment groups. During the extension study, there were no clinically meaningful changes in weight, with mean ±SD changes of -0.4 ± 2.7 kg, 0.2 ± 3.0 kg and -0.7 ± 3.2 kg in the metformin 1000, linagliptin 2.5 + metformin 500, and linagliptin 2.5 + metformin 1000 groups, respectively.</p>
<p>Gomis et al.⁶⁴ (2011)</p> <p>Linagliptin 5 mg/day</p> <p>vs</p> <p>placebo</p> <p>All patients were receiving pioglitazone 30 mg/day.</p>	<p>DB, DD, MC, PC, PG, RCT</p> <p>Type 2 diabetics 18 to 80 years of age with BMI ≤40 kg/m², who had inadequate glycemic control (HbA_{1c} 7.5 to 11.0%)</p>	<p>N=389</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving an HbA_{1c} <7.0%; proportion of patients with an HbA_{1c} decrease ≥0.5%; change in baseline HbA_{1c} over time; change in baseline FPG, β cell function, and</p>	<p>Primary: Combination therapy significantly decreased HbA_{1c} compared to placebo (-1.06±0.06 vs -0.56±0.09%; treatment difference, -0.51%; 95% CI, -0.71 to -0.30; P<0.0001).</p> <p>Secondary: The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with combination therapy compared to placebo (42.9 vs 30.5%; OR, 2.1; 95% CI, 1.3 to 3.5; P=0.0051).</p> <p>A significantly greater proportion of patients receiving combination therapy had ≥5.0% decrease in HbA_{1c} compared to patients receiving placebo (75.0 vs 50.8%; OR, 3.8; 95% CI, 2.3 to 6.4; P<0.0001).</p> <p>The placebo corrected difference in adjusted mean change from baseline in HbA_{1c} increased over the first 12 weeks (reaching -0.5%), and remained</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			body weight; safety	<p>constant until trial end. Combination therapy resulted in a larger decrease in non-adjusted HbA_{1c} over time compared to placebo (P<0.0001 at each visit).</p> <p>Combination therapy significantly decreased FPG compared to placebo (-1.8±0.1 vs -1.0±0.2 mmol/L; treatment difference, -0.8 mmol/L; P<0.0001).</p> <p>There was no difference in decreases in HOMA-IR between the two treatments (-2.90 vs -2.58; treatment difference, -0.32; 95% CI, -0.77 to 0.13; P=0.16). Similar results were observed with HOMA-B (-2.17 vs -1.44; treatment difference, -0.73; 95% CI, -9.16 to 7.70; P=0.86).</p> <p>Both treatments resulted in weight gain, with the increase being significantly greater with combination therapy (2.3 vs 1.2 kg; treatment difference, 1.1 kg; 95% CI, 0.2 to 2.0; P=0.014).</p> <p>Overall, the proportion of patients who experienced at least one adverse event was similar with both treatments (52.5 vs 53.1%). Most adverse events were of mild to moderate intensity. Hypoglycemia occurred in 1.2 and 0.0% of patients receiving combination therapy and placebo, respectively. Laboratory analyses did not reveal any clinically significant findings.</p>
<p>Rosenstock et al.⁶⁵ (2015)</p> <p>Saxagliptin (SAXA) (5 mg/day) plus dapagliflozin (DAPA) (10 mg/day)</p> <p>vs</p> <p>SAXA (5 mg/day) and placebo</p>	<p>DB, RCT</p> <p>Type 2 diabetics with HbA_{1c} ≥8.0% and ≤12.0% on background metformin extended release ≥1,500 mg/day</p>	<p>N=534</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Adjusted mean change from baseline in 2-h PPG, FPG, and body weight, adjusted mean proportion of patients achieving a therapeutic</p>	<p>Primary: At week 24, the adjusted mean change from the baseline HbA_{1c} was -1.5% with SAXA+DAPA+MET vs -0.9% with SAXA+MET (difference -0.59%, P<0.0001) and -1.2% with DAPA+MET (difference -0.27%, P<0.02).</p> <p>Secondary: The adjusted mean reduction in FPG was greater in the SAXA+DAPA+MET group (-38 ± 2.8 mg/dL) than in the SAXA+MET group (-14 ± 2.9 mg/dL) but similar to the DAPA+MET group (-32 ± 2.8 mg/dL). SAXA+DAPA+MET also resulted in a significantly greater adjusted mean reduction from baseline in PPG versus SAXA+MET (difference, -44 mg/dL; 95% CI, -53.7 to -34.3; P<0.0001) but not versus DAPA+MET (difference, -9 mg/dL; 95% CI, -18.8 to 0.5; P=0.06).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>DAPA (10 mg/day) and placebo</p>			<p>glycemic response, defined as HbA_{1c} <7.0%</p>	<p>Reduction in body weight of 2.1 kg (2.4%) was observed in the SAXA+DAPA+MET group and 2.4 kg (2.8%) in the DAPA+MET group compared with no change in the SAXA+MET group. The proportion of patients achieving HbA_{1c} <7% was 41% with SAXA+DAPA+MET versus 18% with SAXA+MET and 22% with DAPA+MET. Urinary and genital infections occurred in ≤1% of patients receiving SAXA+DAPA+MET. Hypoglycemia was infrequent, with no episodes of major hypoglycemia.</p>
<p>Chacra et al.⁶⁶ (2010)</p> <p>Saxagliptin 2.5 mg QD and glyburide 7.5 to 15 mg daily</p> <p>vs</p> <p>saxagliptin 5 mg QD and glyburide 7.5 to 15 mg daily</p> <p>vs</p> <p>glyburide 2.5 to 15 mg daily and placebo</p>	<p>DB, MC, RCT</p> <p>Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA_{1c} ≥7.5 to ≤10.0%), on a submaximal sulfonylurea dose for ≥2 months before screening, fasting C-peptide ≥1 ng/mL, and BMI ≤40 kg/m²</p>	<p>N=768</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and PPG AUC_{0-3hr}, proportion of patients achieving an HbA_{1c} <7.0%, safety</p>	<p>Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (-0.54 and -0.64 vs 0.08%; P<0.0001 for both).</p> <p>Secondary: Saxagliptin significantly decreased FPG compared to placebo (2.5 mg; P=0.0218 and 5 mg; P=0.002).</p> <p>Saxagliptin significantly decreased PPG AUC_{0-3hr} compared to placebo (-4,296 and -5,000 vs 1,196 (mg/minute)/(dL); P<0.0001 for both).</p> <p>A significantly greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (22.4 and 22.8 vs 9.1%; P<0.0001 for both).</p> <p>Overall saxagliptin was well tolerated. The proportion of patients reporting any adverse event was similar across all treatments; with no evidence of a dose-response relationship. The proportion of patients reporting at least one adverse event and at least one treatment-related adverse event was 75.0 and 19.8, 72.3 and 21.3, and 76.8 and 14.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. No events of Stevens-Johnson syndrome or angioedema were reported. Cardiac disorder events were: 2.0, 4.0 and 3.7% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. Hypertension was reported in 3.6, 6.3, and 2.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo; however, mean SBP and DBP decreased with all treatments. There was no difference in the incidence of reported and confirmed hypoglycemic events with saxagliptin compared to placebo (P>0.05). Confirmed hypoglycemia occurred in 2.4, 0.8, and 0.7% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Barnett et al.⁶⁷ (2012)</p> <p>Saxagliptin 5 mg QD</p> <p>vs</p> <p>placebo</p> <p>All patients also received insulin alone or in combination with metformin.</p>	<p>DB, MC, RCT</p> <p>Type 2 diabetics with inadequate glycemic control (HbA_{1c} 7.5 to 11.0% on stable insulin therapy (30 to 150 U/day alone or in combination with metformin) for at least 8 weeks</p>	<p>N=455</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 24 (or rescue), PPG, FPG, body weight, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: Patients treated with saxagliptin had significantly greater reductions in adjusted mean HbA_{1c} (difference, -0.41%; P<0.0001), PPG 180-minute AUC (-3829.8 mg/minute/dL; P=0.0011), and 120-minute PPG (-23.0 mg/dL; P=0.0016) at 24 weeks compared to placebo.</p> <p>Treatment with saxagliptin resulted in similar reductions in HbA_{1c} relative to placebo, irrespective of metformin treatment. At 24 weeks, difference in adjusted mean FPG for saxagliptin compared to placebo was -4.02 mg/dL (P=0.3958); 17.3 and 6.7% of patients in the saxagliptin and placebo groups, respectively, achieved HbA_{1c} <7.0%.</p> <p>Mean change from baseline in body weight at week 24 was 0.39 kg for saxagliptin and 0.18 kg for placebo. Hypoglycemia was reported in 18.4% and 19.9% of patients in the saxagliptin and placebo groups, respectively. Other adverse events reported in at least 5% of patients were urinary tract infection (5.9 vs 6.0%), influenza (3.0 vs 6.6%), and pain in extremity (1.6 vs 6.0%).</p> <p>Secondary: Not reported</p>
<p>Stenlöf et al.⁶⁸ (2010)</p> <p>Saxagliptin 5 mg QD</p> <p>vs</p> <p>placebo</p> <p>All patients also received metformin ER ≥1,500 mg/day.</p>	<p>DB, MC, PC, RCT</p> <p>Type 2 diabetics with inadequate glycemic control (HbA_{1c} 7.0 to 10.0%), and currently receiving stable doses of metformin IR or metformin ER (≥1,500 mg/day) as monotherapy for ≥8 weeks</p>	<p>N=93</p> <p>4 weeks</p>	<p>Primary: Change in baseline 24-hour mean weighted glucose</p> <p>Secondary: Change in baseline four-hour mean weighted PPG, two-hour PPG (both assessed after the evening meal), three-day average mean daily glucose, and two-day average FPG</p>	<p>Primary: Saxagliptin significantly decreased 24-hour mean weighted glucose compared to placebo (-13.8 vs -3.0 mg/dL; P<0.0001).</p> <p>Secondary: Saxagliptin significantly decreased four-hour mean weighted PPG compared to placebo (-30.7 vs 0.4 mg/dL; P<0.0001). Similar results were observed with two-hour mean weighted PPG (-38.2 vs -2.8 mg/dL; P=0.0010).</p> <p>Saxagliptin significantly decreased three-day average mean daily glucose compared placebo (-11.7 vs 7.0 mg/dL; P<0.0001).</p> <p>Saxagliptin significantly decreased two-day average FPG compared to placebo (-10.8 vs 4.5 mg/dl; P=0.002).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Barnett et al.⁶⁹ (2012)</p> <p>Saxagliptin 5 mg QD</p> <p>vs</p> <p>placebo</p> <p>All patients also received insulin alone or in combination with metformin.</p>	<p>DB, MC, RCT</p> <p>Type 2 diabetics with inadequate glycemic control (HbA_{1c} 7.5 to 11.0% on stable insulin therapy (30 to 150 U/day alone or in combination with metformin) for at least 8 weeks</p>	<p>N=455</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 24 (or rescue), PPG, FPG, body weight, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: Patients treated with saxagliptin had significantly greater reductions in adjusted mean HbA_{1c} (difference, -0.41%; P<0.0001), PPG 180-minute AUC (-3829.8 mg/minute/dL; P=0.0011), and 120-minute PPG (-23.0 mg/dL; P=0.0016) at 24 weeks compared to placebo.</p> <p>Treatment with saxagliptin resulted in similar reductions in HbA_{1c} relative to placebo, irrespective of metformin treatment. At 24 weeks, difference in adjusted mean FPG for saxagliptin compared to placebo was -4.02 mg/dL (P=0.3958); 17.3 and 6.7% of patients in the saxagliptin and placebo groups, respectively, achieved HbA_{1c} <7.0%.</p> <p>Mean change from baseline in body weight at week 24 was 0.39 kg for saxagliptin and 0.18 kg for placebo. Hypoglycemia was reported in 18.4% and 19.9% of patients in the saxagliptin and placebo groups, respectively. Other adverse events reported in at least 5% of patients were urinary tract infection (5.9 vs 6.0%), influenza (3.0 vs 6.6%), and pain in extremity (1.6 vs 6.0%).</p> <p>Secondary: Not reported</p>
<p>Matthaei et al.⁷⁰ (2015)</p> <p>Saxagliptin 5 mg/day</p> <p>vs</p> <p>placebo</p> <p>in addition to background dapagliflozin plus metformin IR</p>	<p>DB, RCT</p> <p>Patients on stable metformin (≥1,500 mg/day) for ≥8 weeks with HbA_{1c} 8.0 to 11.5%</p> <p>At screening patients received open-label dapagliflozin (10 mg/day) plus metformin immediate release (IR) for 16 weeks</p>	<p>N=315</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: FPG, proportion of patients achieving HbA_{1c} <7.0%</p>	<p>Primary: Change from baseline in HbA_{1c} was significantly greater with saxagliptin (-0.51%; 95% CI, -0.63 to -0.39) compared with placebo (-0.16%; 95% CI, -0.28 to -0.04) add-on to dapagliflozin plus metformin (difference -0.35%; 95% CI, -0.52 to -0.18; P<0.0001).</p> <p>Secondary: Reductions in 2-h PPG and FPG were similar between treatment arms. A larger proportion of patients achieved HbA_{1c} <7% with saxagliptin add-on to dapagliflozin plus metformin (35.3%) compared with placebo add-on to dapagliflozin plus metformin (23.1%).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>Patients with inadequate glycemic control (HbA_{1c} 7 to 10.5%) after initial 16 weeks were randomized to receive saxagliptin or placebo</p>			
<p>Schernthaner et al.⁷¹ (2015) GENERATION Saxagliptin 5 mg/day vs glimepiride ≤6 mg/day</p>	<p>DB, MC, RCT Patients with type 2 diabetes ≥65 years of age on stable metformin monotherapy at any dose for ≥8 weeks before enrolment and had an HbA_{1c} concentration of 7.0 to 9.0%</p>	<p>N=720 52 weeks</p>	<p>Primary: HbA_{1c} <7.0% without confirmed/severe hypoglycaemia Secondary: Incidence of confirmed/severe hypoglycaemia</p>	<p>Primary: The proportions of patients achieving HbA_{1c} <7.0% at week 52 without confirmed/severe hypoglycaemia were similar with saxagliptin and glimepiride: 37.9 vs 38.2% (OR, 0.99; 95% CI, 0.73 to 1.34; P=0.9415); however, a significant treatment-by-age interaction was detected (P=0.0389). Secondary: Fewer patients in the saxagliptin group experienced ≥1 confirmed/severe hypoglycaemic event over the treatment period, compared with the glimepiride group: 1.1 vs 15.3% (OR, 0.06; 95% CI, 0.02 to 0.17; nominal P<0.0001).</p>
<p>Hermans et al.⁷² (2012) PROMPT Fixed-dose metformin 1500 mg/day, plus either: Add-on saxagliptin 5 mg/day (SAXA-MET) vs metformin</p>	<p>DB, RCT metformin-tolerant patients ≥18 years of age with type 2 diabetes and insufficient glycemic control on submaximal metformin therapy</p>	<p>N=286 24 weeks</p>	<p>Primary: Absolute change from baseline in HbA_{1c} Secondary: Proportion of patients achieving a therapeutic glycemic response, change from baseline in FPG, safety and tolerability</p>	<p>Primary: Compared with baseline, an adjusted mean change in HbA_{1c} at Week 24 of -0.47% was observed in the SAXA-MET group and -0.38% in the MET-UP group. The difference in adjusted mean change from baseline HbA_{1c} between treatment groups was -0.10%, which was not statistically significant (P=0.260). Secondary: The proportion of patients achieving therapeutic glycemic response (HbA_{1c} <7%) at Week 24 was 43.8% (SAXA-MET) and 35.0% (MET-UP). In comparison, the proportion of patients achieving therapeutic glycemic response (HbA_{1c} ≤6.5%) at Week 24 was 20.5% (SAXA-MET) and 16.8% (MET-UP). During the 24-week treatment period, 51.0% (75/147) of patients in the SAXA-MET group and 43.9% (61/139) in the MET-UP group</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
uptitration (MET-UP) to a max dose (2500 mg/day)				experienced at least one adverse event.
DeFronzo et al. ⁷³ (2009) Saxagliptin 2.5 to 10 mg QD and metformin (existing therapy) vs metformin (existing therapy) and placebo	DB, PC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA _{1c} ≥7.0 to ≤10.0%), receiving stable doses of metformin (≥1,500 to <2,550 mg/day) ≥8 weeks, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m ²	N=743 24 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG and PPG AUC _{0-3hr} , proportion of patients achieving an HbA _{1c} <7.0%	Primary: Saxagliptin significantly decreased HbA _{1c} compared to placebo (-0.59, -0.69, and -0.58 vs 0.13%; P<0.0001 for all), with significance achieved after four weeks. Secondary: Saxagliptin significantly decreased FPG compared to placebo (-14.31, -22.03, and -20.50 vs 1.24 mg/dL; P<0.0001 for all). Similar results were observed with PPG AUC _{0-3hr} (-8,891, -9,586, and -8,137 vs -3,291 [mg/minute]/[dL]; P<0.0001 for all). A significantly greater proportion of patients achieved an HbA _{1c} <7.0% with saxagliptin compared to placebo (37.1, 43.5, and 44.4 vs 16.6%; P<0.0001 for all).
Pfutzner et al. ⁷⁴ (2011) Saxagliptin 5 and 10 mg QD plus metformin 500 mg/day vs saxagliptin 10 mg QD vs metformin 500 mg/day	AC, DB, ES, MC, RCT Type 2 diabetics 18 to 77 years of age, HbA _{1c} ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m ²	N=1,306 52 weeks (76 weeks total)	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline body weight, proportion of patients achieving an HbA _{1c} <7.0 and ≤6.5%	Primary: Decreases in HbA _{1c} with saxagliptin 5 mg plus metformin were -2.31% (95% CI -2.44 to -2.18) and -2.33% (95% CI -2.46 to -2.20) with saxagliptin 10 mg plus metformin compared to -1.55 (95% CI, -1.70 to -1.40) and -1.79% (95% CI, -1.93 to -1.65) with saxagliptin and metformin monotherapies, respectively; P<0.0001 for combination therapy vs monotherapy). Secondary: Decreases in body weight were -1.2 kg with saxagliptin 5 mg plus metformin, -0.7 kg with saxagliptin 10 mg plus metformin, -0.3 kg with saxagliptin, and -1.0 kg with metformin (P values not reported). A greater proportion of patients achieved an HbA _{1c} <7.0% with saxagliptin 5 mg plus metformin and saxagliptin 10 mg plus metformin compared to saxagliptin and metformin (51.5 and 50.5 vs 25.0 and 34.7%, respectively; P values not reported). Similar results were observed with HbA _{1c} <6.5% (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Jadzinsky et al.⁷⁵ (2009)</p> <p>Saxagliptin 5 mg QD plus metformin 500 to 2,000 mg daily</p> <p>vs</p> <p>saxagliptin 10 mg QD plus metformin 500 to 2,000 mg daily</p> <p>vs</p> <p>saxagliptin 10 mg QD</p> <p>vs</p> <p>metformin 500 to 2,000 mg daily</p>	<p>AC, DB, MC, RCT</p> <p>Type 2 diabetics 18 to 77 years of age, HbA_{1c} ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m²</p>	<p>N=1,306</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and PPG AUC_{0-3hr}, proportion of patients achieving an HbA_{1c} <7.0 and ≤6.5%, proportion of patients requiring rescue for failing to achieve prespecified glycemic targets or discontinuing for lack of efficacy at 24 weeks</p>	<p>Primary: Combination therapy significantly decreased HbA_{1c} compared to monotherapy with either saxagliptin or metformin (-2.5 and -2.5 vs -1.7 and -2.0%, respectively; P<0.0001 vs monotherapy for all).</p> <p>Secondary: Combination therapy significantly decreased FPG compared to monotherapy with either saxagliptin or metformin (P=0.0002 for saxagliptin 5 mg plus metformin vs saxagliptin and P<0.001 for saxagliptin 10 mg plus metformin vs saxagliptin and metformin). Similar results were observed for PPG AUC_{0-3hr} (P<0.0001 for all vs monotherapy).</p> <p>The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with combination therapy compared to monotherapy with either agent (60.3 and 59.7 vs 32.2 and 41.1%; P<0.0001 for all vs monotherapy). Similar results were observed for HbA_{1c} ≤6.5% (45.3 and 40.6 vs 20.3 and 29.0%; P<0.0001 for saxagliptin 5 mg plus metformin vs saxagliptin and metformin; P<0.0001 for saxagliptin 10 mg plus metformin vs saxagliptin, and P=0.0026 for saxagliptin 10 mg plus metformin vs metformin).</p> <p>At week 24, 7.5% of patients receiving saxagliptin 5 mg plus metformin and 21.2% of patients receiving saxagliptin 10 mg were discontinued or rescued for lack of glycemic control (P<0.0001). No significance was observed when saxagliptin 5 mg plus metformin was compared to metformin (P=0.2693). Similar results were observed with saxagliptin 10 mg plus metformin compared to either monotherapy (P<0.0001 vs saxagliptin 10 mg and P=0.0597 vs metformin).</p>
<p>Hollander et al.⁷⁶ (2009)</p> <p>Saxagliptin 2.5 mg and TZD (existing therapy)</p> <p>vs</p>	<p>DB, MC, RCT</p> <p>Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.5%) receiving</p>	<p>N=565</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and PPG AUC_{0-3hr},</p>	<p>Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (saxagliptin 2.5 mg, -0.66%; treatment difference, -0.36%; P<0.0007 vs placebo and saxagliptin 5 mg, -0.94%; treatment difference, -0.63%; P<0.0001 vs placebo).</p> <p>Secondary: Saxagliptin significantly decreased FPG compared to placebo (saxagliptin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
saxagliptin 5 mg and TZD (existing therapy) vs TZD (existing therapy) and placebo	stable doses of TZD (pioglitazone 30 or 45 mg/day or rosiglitazone 4 or 8 mg/day for ≥ 12 weeks), fasting C-peptide ≥ 0.3 nmol/L, and BMI ≤ 45 kg/m ²		proportion of patients achieving an HbA _{1c} <7.0%	2.5 mg treatment difference, -0.8 mmol/L; P<0.0053 vs placebo and saxagliptin 5 mg treatment difference, -1.0 mmol/L; P=0.0005 vs placebo). A significantly greater proportion of patients receiving saxagliptin achieved an HbA _{1c} <7.0% compared to patients receiving placebo (42.2 [P=0.0010] and 41.8 [P=0.0013] vs 25.6%). Saxagliptin significantly decreased PPG AUC _{0-3hr} compared to placebo (P<0.0001 for both). Similar results were observed with PPG AUC _{0-2hr} (P<0.0001 for both). Overall, saxagliptin was well tolerated. The proportion of patients experiencing any adverse effect was 68.0 vs 66.8%, with the highest frequency with saxagliptin 5 mg. The frequency of hypoglycemic events was similar between the two treatments (3.4 vs 3.8%). The most commonly reported adverse events were upper respiratory tract infection, peripheral edema, and headache.
Frederich et al. ⁷⁷ (2010) Saxagliptin 2.5 to 10 mg QD vs glyburide, metformin, or placebo	SR Inadequately controlled type 2 diabetics	N=4,607 16 to 116 weeks	Primary: Composite of cardiovascular events, cardiovascular death, MI, and stroke Secondary: Not reported	Primary: There were 38 (1.1%) cardiovascular events with saxagliptin compared to 23 (1.8%) with the comparator drugs (RR, 0.59; 95% CI, 0.35 to 1.00). There were 23 (0.7%) cardiovascular deaths, MIs, and stroke events with saxagliptin compared to 18 (1.4%) with the comparator drugs (RR, 0.44; 95% CI, 0.24 to 0.82). There were seven (0.2%) cardiovascular deaths with saxagliptin compared to 10 (0.8%) with comparator drugs (RR, 0.24; 95% CI, 0.09 to 0.63). Secondary: Not reported
Scheen et al. ⁷⁸ (2010) Saxagliptin 5 mg QD vs	AC, DB, MC, PG, RCT Type 2 diabetics ≥ 18 years of age, with uncontrolled HbA _{1c} (6.5 to 10.0%) despite	N=801 18 weeks	Primary: Change in baseline HbA _{1c} Secondary: Proportion of patients achieving an HbA _{1c} $\leq 6.5\%$;	Primary: Saxagliptin was non-inferior to sitagliptin (-0.52 vs -0.62%). The adjusted mean decrease in HbA _{1c} was 0.09% (95% CI, -0.01 to 0.20), with the upper limit for non-inferiority <0.3%. Secondary: A higher proportion of patients receiving sitagliptin achieved HbA _{1c} $\leq 6.5\%$ compared to patients receiving saxagliptin (29.1 vs 26.3%; P value

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>sitagliptin 100 mg QD</p> <p>Patients also received metformin.</p>	<p>monotherapy with a stable dose of metformin $\geq 1,500$ mg for ≥ 8 weeks</p>		<p>proportion of patients with baseline HbA_{1c} $\geq 7.0\%$ achieving an HbA_{1c} $< 7.0\%$; change in baseline FPG, insulin, C-peptide, proinsulin, and β cell function</p>	<p>not reported).</p> <p>For patients with baseline HbA_{1c} $\geq 7.0\%$, a non-significantly higher proportion of patients receiving sitagliptin achieved an HbA_{1c} $< 7.0\%$ compared to patients receiving saxagliptin (39.1 vs 33.0%; treatment difference, -6.1%; 95% CI, -13.8 to 1.6%).</p> <p>Sitagliptin significantly decreased FPG compared to saxagliptin (-16.2 vs -10.8 mg/dL; treatment difference, -5.42 mg/dL; 95% CI, 1.37 to 9.47).</p> <p>There were no apparent differences between the two treatments for the changes in fasting insulin, glucagon, proinsulin, or C-peptide. Similarly, the small improvement in β cell function did not differ between the two treatments.</p>
<p>Göke et al.⁷⁹ (2010)</p> <p>Saxagliptin 5 mg/day</p> <p>vs</p> <p>glipizide 5 mg/day, titrated up to 20 mg/day</p>	<p>DB, NI, RCT</p> <p>Patients ≥ 18 years of age with type 2 diabetes with type 2 diabetes, HbA_{1c} > 6.5 to 10.0%, and inadequate glycemic control on metformin alone</p>	<p>N=858</p> <p>52 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Hypoglycemia, safety</p>	<p>Primary: The per protocol analysis demonstrated non-inferiority of saxagliptin vs glipizide; adulated mean changes from baseline HbA_{1c} were -0.74 vs -0.80%, respectively; the between-group difference was 0.06% (95% CI, -0.05 to 0.16).</p> <p>There was a significantly smaller risk in HbA_{1c} (%/week) from week 24 to 52 with saxagliptin vs glipizide (0.001 vs 0.004%; $P=0.04$) indicating a sustained glycemic effect beyond week 24.</p> <p>Secondary: Treatment with saxagliptin vs glipizide was associated with a significantly smaller proportion of patients with hypoglycemic events (3.0 vs 36.3%; $P<0.0001$) and a divergent impact on body weight (adjusted mean change from baseline, -1.1 vs 1.1 kg; $P<0.0001$).</p> <p>Excluding hypoglycemic events, the proportion of patients reporting adverse events was smaller with glipizide (60.0 vs 56.7%); however, treatment-related adverse events were less common with saxagliptin (9.8 vs 31.2%), attributable to the higher frequency of hypoglycemia with glipizide. Discontinuation rates resulting from adverse events were similar (approximately 4%).</p>
<p>Göke et al.⁸⁰</p>	<p>AC, DB, MC, RCT</p>	<p>N=858</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2013)</p> <p>Saxagliptin 5 mg/day</p> <p>vs</p> <p>glipizide 5 to 20 mg/day</p> <p>Both treatments as an add-on to metformin</p>	<p>Adults with type 2 diabetes and inadequate glycemic control on metformin alone ($HbA_{1c} > 6.5$ to 10%)</p>	<p>52 week initial phase followed by 52 week extension phase</p>	<p>Non-inferiority in mean change from baseline HbA_{1c}, safety and tolerability</p> <p>Secondary: Not reported</p>	<p>Improvement in HbA_{1c} at week 104 was similar with saxagliptin + metformin and glipizide + metformin. At week 104, the adjusted mean \pmSE change from baseline HbA_{1c} was $-0.41 \pm 0.04\%$ with saxagliptin + metformin and $-0.35 \pm 0.04\%$ with glipizide + metformin [a between-group difference of -0.05% (95% CI, -0.17 to 0.06%)].</p> <p>Over the course of the 104-week study, 896 hypoglycemic events were reported in 165 patients (38.4%) in the glipizide + metformin group, and 24 hypoglycemic events were reported in 15 patients (3.5%) in the saxagliptin + metformin group (difference, -34.9%; 95% CI for difference, -39.8 to -30.0%). Most of these events occurred during the initial 52 weeks.</p> <p>Over the course of the study, mean body weight decreased in the saxagliptin + metformin group and increased in the glipizide + metformin group.</p> <p>Secondary: Not reported</p>
<p>Harashima et al.⁸¹ (2012)</p> <p>Sitagliptin 100 mg QD</p> <p>All patients received existing sulfonylurea therapy.</p>	<p>PRO, SA</p> <p>Type 2 diabetics ≥ 20 years of age inadequately controlled on sulfonylureas, with or without metformin and/or α-glucosidase inhibitors, $HbA_{1c} \geq 6.9\%$, no improvement in $HbA_{1c} \geq 0.5\%$ within 3 months, and a wish to diet and exercise to improve health</p>	<p>N=82</p> <p>52 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Changes in BMI, BP, urinary albumin excretion, unresponsive rate, hypoglycemia</p>	<p>Primary: Change in HbA_{1c} was -0.80% (95% CI, -0.90 to -0.68; $P < 0.001$).</p> <p>Secondary: Change in BMI, SBP, DBP, and urinary albumin excretion were -0.38 kg/m^2 (95% CI, -0.72 to -0.04; $P < 0.05$), $-6.7/-3.6$ mm Hg (95% CI, -10.0 to $-3.4/-4.8$ to -2.4; $P < 0.001$), and -43.2 mg/gCr (95% CI, -65.7 to -20.8; $P < 0.001$), respectively.</p> <p>The unresponsive rate was 6.1%.</p> <p>Mild hypoglycemia was observed in three cases.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Brazg et al.⁸² (2007)</p> <p>Sitagliptin 50 mg BID</p> <p>vs</p> <p>placebo</p> <p>All patients were receiving metformin $\geq 1,500$ mg daily.</p>	<p>DB, PC, RCT, XO</p> <p>Type 2 diabetics 25 to 75 years of age with inadequate glycemic control receiving metformin monotherapy, and an HbA_{1c} of 6.5 to 9.6%</p>	<p>N=28</p> <p>8 weeks</p>	<p>Primary: 24-hour weighted mean glucose</p> <p>Secondary: Change in FPG, mean daily glucose, fructosamine, and β cell function; safety</p>	<p>Primary: Sitagliptin (-32.8 mg/dL) significantly decreased 24-hour weighted mean glucose compared to placebo (P<0.05).</p> <p>Secondary: Despite a carryover effect from Period 1 to 2, the combined Period 1 and 2 results for glycemic measurements were significant with sitagliptin compared to placebo. The Period 1 results were also compared between the groups, in consideration of any carryover.</p> <p>Following Period 1, there were significant decreases in FPG of -20.3 mg/dL, mean daily glucose of -28 mg/dL, and fructosamine of -33.7 mmol/L with sitagliptin compared to placebo (P<0.05).</p> <p>Sitagliptin significantly improved β cell function compared to placebo.</p> <p>There was no difference in weight gain, gastrointestinal adverse events, and hypoglycemia between the two treatments.</p>
<p>Charbonnel et al.⁸³ (2006)</p> <p>Sitagliptin 100 mg QD</p> <p>vs</p> <p>placebo</p> <p>All patients were receiving metformin $\geq 1,500$ mg daily.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetics 18 to 78 years of age with inadequate glycemic control (HbA_{1c} ≥ 7.0 to $\leq 10.0\%$) on metformin monotherapy</p>	<p>N=701</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, PPG, insulin, C-peptide concentrations, β cell function, and lipid profile; safety</p>	<p>Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.65%; P<0.001). A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% (47.0 vs 18.3%; P<0.001) and <6.5% (17.2 vs 4.9%; P<0.001) compared to patients receiving placebo.</p> <p>Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -25.4 mg/dL; P<0.001). Similar results were observed with PPG (treatment difference, -50.6 mg/dL; P\leq0.001).</p> <p>Sitagliptin significantly increased fasting insulin (P<0.050) and fasting C-peptide (P<0.010) compared to placebo. There was observed improvement in fasting proinsulin:insulin ratio (P<0.010) and HOMA-B (P<0.001) consistent with improved β cell function with sitagliptin.</p> <p>There were differences between the two treatments in changes in LDL-C.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>There were no differences between two treatments in the incidences of overall or serious adverse reactions, rates of hypoglycemia, or gastrointestinal adverse events. A reduction in weight of 0.6 to 0.7 kg was observed with both treatment groups ($P<0.050$), but there was no difference between the two treatments ($P=0.835$).</p>
<p>Derosa et al.⁸⁴ (2014)</p> <p>Sitagliptin 100 mg/day</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, RCT</p> <p>Caucasian patients with type 2 diabetes aged >18 with uncontrolled type 2 diabetes mellitus ($HbA_{1c} >7.0\%$) in therapy with different antidiabetic drugs for at least 6 months</p>	<p>N=205</p> <p>2 years</p>	<p>Primary: Body weight, BMI, HbA_{1c}, FPG, PPG, lipids</p> <p>Secondary: Not reported</p>	<p>Primary: In the sitagliptin group, there was a significant decrease in body weight and BMI compared with baseline and with placebo ($P<0.05$, for both). HbA_{1c} significantly decreased after 24 months compared with baseline ($P<0.01$), while HbA_{1c} increased in the placebo group ($P<0.05$). These results were mirrored in the FPG and PPG parameters.</p> <p>Total cholesterol (TC) and LDL-C significantly decreased after 18 ($P<0.05$) and 24 months ($P<0.02$) after the addition of sitagliptin, while no variations were registered with placebo. Moreover, TC and LDL-C observed with sitagliptin were significantly lower than the ones recorded with placebo after 24 months.</p> <p>Secondary: Not reported</p>
<p>Green et al.⁸⁵ (2015)</p> <p>Sitagliptin 100 mg/day</p> <p>vs</p> <p>placebo</p> <p>Open-label use of antihyperglycemic therapy was encouraged as required</p>	<p>DB, MC, RCT</p> <p>Patients with type 2 diabetes and established cardiovascular disease who were at least 50 years of age, with a HbA_{1c} of 6.5 to 8.0% when treated with stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or</p>	<p>N=14,671</p> <p>Median of 3.0 years</p>	<p>Primary: Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina</p> <p>Secondary: Composite of the first confirmed event of cardiovascular death, nonfatal myocardial</p>	<p>Primary: Overall in the intention-to-treat population, the primary composite cardiovascular outcome occurred in 839 patients in the sitagliptin group (11.4%, 4.06 per 100 person-years) and 851 in the placebo group (11.6%, 4.17 per 100 person-years). There was no significant between-group difference in the primary composite cardiovascular outcome (HR in the per-protocol analysis, 0.98; 95% CI, 0.88 to 1.09; $P<0.001$ for noninferiority; HR in the intention-to-treat analysis, 0.98; 95% CI, 0.89 to 1.08; $P=0.65$ for superiority).</p> <p>Secondary: There was no significant between-group difference in the secondary composite cardiovascular outcome (HR in the per-protocol analysis, 0.99; 95% CI, 0.89 to 1.11; $P<0.001$ for noninferiority; HR in the intention-to-treat analysis, 0.99; 95% CI, 0.89 to 1.10; $P=0.84$ for superiority).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	insulin (with or without metformin)		infarction, or nonfatal stroke	
Raz et al. ⁸⁶ (2008) Sitagliptin 100 mg daily plus metformin 1,500 to 2,550 mg daily (existing therapy) vs metformin 1,500 to 2,550 mg daily (existing therapy) plus placebo	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age, HbA _{1c} 7.0 to 10.0% receiving metformin or other oral antihyperglycemic agents as monotherapy or being treated with metformin in combination with other oral antihyperglycemic agents	N=190 30 weeks	Primary: Change in baseline HbA _{1c} at 18 weeks Secondary: Change in baseline FPG at 18 weeks, two-hour PPG at 18 weeks, and HbA _{1c} at 30 weeks; safety and tolerability	Primary: Sitagliptin significantly decreased HbA _{1c} compared to placebo (treatment difference, -1.0%; 95% CI, -1.4 to -0.7; P<0.001). Numerically greater decreases in HbA _{1c} were observed in patients with a higher baseline HbA _{1c} . A greater proportion of patients receiving sitagliptin achieved an HbA _{1c} <7.0% at weeks 18 and 30 compared to patients receiving placebo (13.7 and 22.1 vs 3.3 and 3.3%; P values not reported). Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -1.4 mmol/L; 95% CI, -2.1 to -0.7; P<0.001). Sitagliptin significantly decreased two-hour PPG compared to placebo (treatment difference, -3.0 mmol/L; 95% CI, -4.2 to -1.9; P<0.001). Sitagliptin significantly decreased HbA _{1c} compared to placebo at week 30 (treatment difference, -1.0%; 95% CI, -1.4 to -0.6; P<0.001). The incidence of adverse events was similar with both treatments. No serious adverse events or discontinuations due to clinical adverse events were reported with sitagliptin. With placebo, there were six serious clinical adverse events that resulted in one death and two discontinuations. None of the adverse events were deemed to be drug-related. There were no differences between the two treatments in the incidences of hypoglycemia or gastrointestinal adverse events (abdominal pain, nausea, vomiting, and diarrhea). Over the 30 week period a small decrease in weight of 0.5 kg was observed with both treatments.
Derosa et al. ⁸⁷ (2012) metformin + placebo vs	DB, MC, PC, RCT Type 2 diabetic patients aged >18, drug-naïve, with poor glycemic control (HbA _{1c} level >8.0%), and	N=178 12 months	Primary: BMI, glycemic control, fasting plasma insulin (FPI), homeostasis model assessment insulin resistance index (HOMA-IR),	Primary: A similar decrease of body weight and BMI was observed with both treatments at 12 months (P<0.05 for both), without any difference between the two groups. HbA _{1c} and PPG improved in both groups at six (P<0.05), nine (P<0.01), and 12 months (P<0.001) with sitagliptin + metformin, and at nine (P<0.05) and 12 months (P<0.01) with placebo + metformin, even though

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>metformin + sitagliptin</p> <p>All patients underwent a run-in period of 8±2 months of metformin monotherapy</p>	<p>overweight (body mass index [BMI] ≥25 and <30 kg/m²)</p>		<p>homeostasis model assessment β-cell function index (HOMA-β), fasting plasma proinsulin (FPPr), proinsulin/fasting plasma insulin ratio (Pr/FPI ratio), C-peptide, glucagon, adiponectin (ADN), and high sensitivity-C reactive protein (Hs-CRP).</p> <p>Secondary: Not reported</p>	<p>sitagliptin + metformin were more effective than placebo + metformin in reducing HbA_{1c}, and PPG at 12 months (P<0.05). FPG obtained with sitagliptin + metformin was significantly lower compared to the value reached with placebo + metformin at 12 months (P<0.05).</p> <p>Most other parameters achieved favorable change from baseline but no significant difference between treatment groups. Sitagliptin + metformin resulted better than placebo + metformin in reducing HOMA-IR and glucagon at 12 months (P<0.05).</p> <p>Secondary: Not reported</p>
<p>Goldstein et al.⁸⁸ (2007)</p> <p>Sitagliptin 50 mg BID plus metformin 500 mg BID</p> <p>vs</p> <p>sitagliptin 50 mg BID plus metformin 1,000 mg BID</p> <p>vs</p> <p>sitagliptin 100 mg</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetics 18 to 78 years of age and an HbA_{1c} of 7.5 to 11.0%</p>	<p>N=1,091</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, lipid profiles, β cell function, insulin resistance; adverse events</p>	<p>Primary: Decreases in HbA_{1c} were significant with all active treatments as compared to placebo and for combination therapy compared to monotherapy (P<0.001). There was an additive effect seen in the combination treatment groups. The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with all active treatments compared to placebo (P<0.001).</p> <p>Secondary: Significant decreases in FPG were achieved between combination therapy and monotherapy, and between all active treatments compared to placebo (P<0.001).</p> <p>Data on fasting serum insulin and lipid profiles were not reported.</p> <p>Combination therapy demonstrated an additive effect, as compared to monotherapy, with regards to improvements in β cell function.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>QD</p> <p>vs</p> <p>metformin 500 mg BID</p> <p>vs</p> <p>metformin 1,000 mg BID</p> <p>vs</p> <p>placebo</p>				<p>HOMA-B increased with all active treatments compared to placebo (P<0.001). The combination therapy significantly increased HOMA-B compared to monotherapy (sitagliptin and low-dose metformin; P≤0.001).</p> <p>Significant improvements in the proinsulin:insulin ratio observed with all active treatments compared to placebo (P<0.05). Differences between combination therapy and monotherapy were also significant (P<0.05).</p> <p>The incidence of adverse events was similar between combination therapy and metformin. Gastrointestinal adverse events including diarrhea, nausea, abdominal pain, and vomiting were most frequently observed with metformin high-dose both as monotherapy and combination therapy. A low frequency of hypoglycemia was similar among all treatments (0.6 to 2.2%). No change in weight was observed with sitagliptin compared to all other active treatments, where there was a significant decrease in body weight (-0.6 to -1.3 kg; P<0.05) and placebo (-0.9 kg; P<0.01).</p>
<p>Reasner et al.⁸⁹ (2011)</p> <p>Sitagliptin/metformin 50/500 to 1,00 mg BID</p> <p>vs</p> <p>metformin 500 to 1,000 mg BID</p>	<p>DB, MC, PG, RCT</p> <p>Treatment-naïve type 2 diabetics 18 to 78 years of age, and an HbA_{1c} ≥7.5%</p>	<p>N=1,250</p> <p>18 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving an HbA_{1c} <7.0 and <6.5%, change in baseline FPG, proinsulin:insulin ratio, and β cell function</p>	<p>Primary: Combination therapy significantly decreased HbA_{1c} compared to metformin (-2.4 vs -1.8%; P<0.001).</p> <p>Secondary: A significantly greater proportion of patients receiving combination therapy achieved an HbA_{1c} <7.0% (49.2 vs 34.2%, respectively; P<0.001) and <6.5% (31.8 vs 16.0%, respectively; P<0.001) compared to patients receiving metformin.</p> <p>Combination therapy significantly decreased FPG compared to metformin (-3.8 vs -3.0 mg/dL; P<0.001).</p> <p>Combination therapy significantly decreased proinsulin:insulin ratio compared to metformin (-0.238 vs -0.186; P<0.05).</p> <p>Combination therapy significantly improved β cell function compared to metformin (P<0.05).</p>
<p>Rosenstock et al.⁹⁰ (2006)</p>	<p>DB, MC, PC, PG, RCT</p>	<p>N=353</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p>	<p>Primary: Combination therapy (-0.70%; 95% CI, -0.85 to -0.54) significantly decreased HbA_{1c} compared to placebo (P<0.001). A significantly greater</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Sitagliptin 100 mg QD</p> <p>vs</p> <p>placebo</p> <p>All patients were receiving pioglitazone 30 or 45 mg QD.</p>	<p>Type 2 diabetics ≥ 18 years of age with inadequate glycemic control ($HbA_{1c} \geq 7.0$ to $\leq 10.0\%$) on pioglitazone monotherapy</p>		<p>Secondary: Change in baseline FPG, fasting insulin, proinsulin, and lipid profiles; safety and tolerability</p>	<p>proportion of patients receiving combination therapy achieved $HbA_{1c} < 7.0\%$ compared to patients receiving placebo (45 vs 23%; $P < 0.001$).</p> <p>Secondary: Combination therapy significantly decreased FPG compared to placebo (treatment difference, -17.7 mg/dL; 95% CI, -24.3 to -11.0; $P < 0.001$).</p> <p>Combination therapy significantly decreased fasting serum proinsulin ($P = 0.009$) and proinsulin:insulin ratio ($P < 0.001$) compared to placebo.</p> <p>Combination therapy significantly decreased TG compared to placebo (treatment difference, -11.2%; 95% CI, -22.0 to -0.4; $P < 0.041$). There were no significant changes in other lipid parameters.</p> <p>Combination therapy was well tolerated, with no increased risk of hypoglycemia compared to placebo. There was a significant increase in the incidence of abdominal pain with combination therapy compared to placebo. There was no difference in the change of body weight between the two treatments.</p>
<p>Lavalle-González et al.⁹¹ (2013)</p> <p>canagliflozin 100 mg</p> <p>vs</p> <p>canagliflozin 300 mg</p> <p>vs</p> <p>sitagliptin 100 mg</p> <p>vs</p>	<p>DB, PG, RCT</p> <p>Patients with type 2 diabetes aged ≥ 18 and ≤ 80 years who had inadequate glycemic control ($HbA_{1c} \geq 7.0\%$ and $\leq 10.5\%$) on metformin therapy</p>	<p>N=1,284</p> <p>2 week placebo run-in, 26 week placebo- and active-control treatment period (period I), followed by a 26 week active-control treatment period (period II), and a 4 week follow-up period</p>	<p>Primary: Change from baseline in HbA_{1c} at week 26</p> <p>Secondary: Changes in HbA_{1c} (week 52) and FPG, body weight, and systolic blood pressure (BP; weeks 26 and 52), adverse events</p>	<p>Primary: At week 26, canagliflozin 100 mg and 300 mg significantly reduced HbA_{1c} from baseline compared with placebo ($P < 0.001$ for both).</p> <p>Secondary: At week 26, a greater proportion of participants treated with canagliflozin 100 mg and 300 mg achieved $HbA_{1c} < 7.0\%$ than with placebo (45.5, 57.8, and 29.8%, respectively; $P = 0.000$ for both); 54.5% of sitagliptin-treated participants achieved $HbA_{1c} < 7.0\%$. Both canagliflozin doses significantly reduced FPG and 2-hour PPG at week 26 vs placebo ($P < 0.001$ for all); FPG and 2-hour PPG were also reduced from baseline with sitagliptin.</p> <p>At 52 weeks, canagliflozin 100 mg and 300 mg demonstrated non-inferiority to sitagliptin 100 mg in HbA_{1c}-lowering effect. Canagliflozin 300 mg demonstrated statistical superiority to sitagliptin in HbA_{1c}-lowering effect. Canagliflozin 100 mg and 300 mg significantly reduced body weight compared with sitagliptin. Canagliflozin 100 mg and 300 mg significantly decreased systolic BP relative to sitagliptin at 52 weeks. The</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				<p>change in diastolic BP from baseline was -1.8 mmHg with both canagliflozin doses and -0.3 mmHg with sitagliptin.</p> <p>Overall incidences of adverse events and adverse event-related discontinuations were generally comparable across groups over 52 weeks. Canagliflozin was associated with a higher incidence of genital mycotic infections in men and women. These were generally mild or moderate in intensity and led to few discontinuations.</p>
Weinstock et al. ⁹² (2015) AWARD-5 Sitagliptin 100 mg vs dulaglutide (1.5 or 0.75 mg)	<p>DB, MC, RCT</p> <p>Patients 18 to 75 years of age with type 2 diabetes (≥ 6 months' duration) and an HbA_{1c} value of $>8.0\%$ and $\leq 9.5\%$ on diet and exercise alone, or $\geq 7.0\%$ and $\leq 9.5\%$ on monotherapy or combination therapy (metformin plus another oral antihyperglycaemic medication), and a BMI of 25 to 40 kg/m²</p>	<p>N=1,098</p> <p>104 weeks</p>	<p>Primary: HbA_{1c}</p> <p>Secondary: Percentage of participants achieving an HbA_{1c} target of $<7.0\%$ and $\leq 6.5\%$; body weight; FPG and fasting insulin; β-cell function; lipids; safety</p>	<p>Primary: Changes in HbA_{1c} at 104 weeks were (least squares mean \pm standard error) $-0.99 \pm 0.06\%$, $-0.71 \pm 0.07\%$ and $-0.32 \pm 0.06\%$ for dulaglutide 1.5 mg, dulaglutide 0.75 mg and sitagliptin, respectively ($P < 0.001$, both dulaglutide doses vs sitagliptin).</p> <p>Secondary: At 104 weeks, the percentage of participants attaining the HbA_{1c} target goal of $<7.0\%$ was significantly higher in the dulaglutide 1.5 mg and dulaglutide 0.75 mg arms (54 and 45%, respectively) compared with sitagliptin (31%; $P < 0.001$, both comparisons). Additionally, 39 and 24% of participants in the dulaglutide 1.5 mg and dulaglutide 0.75 mg arms, respectively, achieved HbA_{1c} targets of $\leq 6.5\%$, compared with 14% in the sitagliptin arm ($P < 0.001$, both comparisons).</p> <p>The measurement of insulin sensitivity (HOMA2-%S) was not different between treatment groups, while β-cell function, as assessed by HOMA2-%β, increased significantly more with dulaglutide 1.5 mg and dulaglutide 0.75 mg than with sitagliptin. Weight loss was greater with dulaglutide 1.5 mg ($P < 0.001$) and similar with 0.75 mg versus sitagliptin (2.88 ± 0.25, 2.39 ± 0.26 and 1.75 ± 0.25 kg, respectively). Gastrointestinal adverse events were more common with dulaglutide 1.5 and 0.75 mg versus sitagliptin (nausea 17 and 15% vs 7%, diarrhoea 16 and 12% vs 6%, vomiting 14 and 8% vs 4% respectively). Pancreatic, thyroid, cardiovascular and hypersensitivity safety were similar across groups.</p>
Bergenstal et al. ⁹³ (2010) DURATION-2	<p>DB, DD, MC, PG, RCT</p> <p>Type 2 diabetics</p>	<p>N=514</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p>	<p>Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c} compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; $P < 0.0001$) and pioglitazone (-1.2% [95% CI,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Exenatide ER 2 mg SC once weekly</p> <p>vs</p> <p>sitagliptin 100 mg QD</p> <p>vs</p> <p>pioglitazone 45 mg QD</p> <p>All patients received existing metformin therapy.</p>	<p>≥18 years of age, receiving a stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m²</p>		<p>Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported quality of life, safety</p>	<p>-1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165).</p> <p>Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone.</p> <p>Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; P<0.0001), but no difference was observed between patients receiving pioglitazone (52%; P=0.1024).</p> <p>In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported).</p> <p>Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001).</p> <p>Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0).</p> <p>Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 μIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 μIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 μIU/mL [95% CI, 0.6 to 5.8]; P=0.0161) and pioglitazone (-3.9 μIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 μIU/mL [95% CI, 4.9 to 10.1]; P<0.0001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only).</p> <p>All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported).</p> <p>All five domains of weight-related quality of life and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406).</p> <p>The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported.</p>
<p>Nauck et al.⁹⁴ (2007)</p> <p>Sitagliptin 100 mg QD</p> <p>vs</p> <p>glipizide 5 to 20</p>	<p>AC, DB, MC, NI, PG, RCT</p> <p>Patients 18 to 78 years of age with type 2 diabetes who were inadequately controlled (HbA_{1c} ≥6.5 and ≤10%) on</p>	<p>N=1,172</p> <p>52 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, fasting insulin, proinsulin, and lipid parameters, β-cell</p>	<p>Primary: In both treatments, the least squares mean HbA_{1c} change from baseline was -0.67% (95% CI, -0.75 to -0.59).</p> <p>A similar proportion of patients reached an HbA_{1c} <7.0% in each group (63 vs 59%; difference of 3.9%; 95% CI, -2.8 to 10.7).</p> <p>Secondary: The change in FPG was not significantly different between the two</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>mg QD</p> <p>All patients received metformin \geq1,500 mg daily.</p>	<p>metformin monotherapy</p>		<p>function, insulin resistance and sensitivity, safety and tolerability, change in body weight</p>	<p>treatments. The least squares change from baseline for sitagliptin was -0.56 mmol/L (95% CI, -0.81 to -0.30) and -0.42 mmol/L for glipizide (95% CI, -0.67 to -0.17). Sitagliptin led to a decrease in fasting proinsulin compared with an increase with glipizide.</p> <p>Patients receiving glipizide demonstrated a higher rate of hypoglycemia as compared to patients receiving sitagliptin (32 vs 5%; $P < 0.001$). No meaningful differences in overall serious clinical adverse events were observed between the two treatments.</p> <p>Body weight significantly decreased with sitagliptin; the least squares mean change from baseline was -1.5 kg (95% CI, -2 to -0.9). Body weight significantly increased with glipizide with a least squares mean change from baseline of 1.1 kg (95% CI, 0.5 to 1.6). The between-treatment difference was -2.5 kg (95% CI, -3.1 to -2.0; $P < 0.001$).</p>
<p>Hermansen et al.⁹⁵ (2007)</p> <p>Sitagliptin 100 mg QD, glimepiride 4 to 8 mg daily, and metformin 1,500 to 3,000 mg daily</p> <p>vs</p> <p>sitagliptin 100 mg QD plus glimepiride 4 to 8 mg daily</p> <p>vs</p> <p>glimepiride 4 to 8 mg daily, metformin 1,500 to 3,000 mg daily,</p>	<p>DB, DD, MC, PC, PG, RCT</p> <p>Type 2 diabetics 18 to 75 years of age, HbA_{1c} 6.7 to 10.6%, and inadequately controlled on glimepiride with or without metformin</p>	<p>N=441</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, plasma lipids, β cell function, and insulin resistance; safety and tolerability</p>	<p>Primary: Sitagliptin significantly decreased HbA_{1c} ($P < 0.001$) compared to placebo (treatment difference, -0.74%; 95% CI, -0.90 to -0.57). Patients who were receiving triple therapy (-0.89%; 95% CI, -1.10 to -0.68) had a significantly greater decrease in HbA_{1c} compared to patients receiving combination therapy (-0.57%; 95% CI, -0.82 to -0.32).</p> <p>A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} $<$7.0% compared to patients receiving placebo (17.1 vs 4.8%; $P < 0.001$). A significantly greater proportion of patients receiving triple therapy achieved an HbA_{1c} $<$7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; $P < 0.001$). No difference was observed between combination therapy with glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; $P < 0.638$).</p> <p>Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; $P < 0.001$).</p> <p>Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>and placebo</p> <p>vs</p> <p>glimepiride 4 to 8 mg daily plus placebo</p>				<p>A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; P<0.001). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and QUICKI between the treatments.</p> <p>Sitagliptin significantly increased fasting insulin compared to placebo (1.8 vs 0.1 μIU/mL; P<0.001).</p> <p>Sitagliptin was well tolerated, both in combination with glimepiride and in triple therapy. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed with sitagliptin compared to placebo, with the majority of that difference due to rates of minor to moderate hypoglycemia.</p> <p>A significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted with sitagliptin compared to a slight decrease in weight with placebo (-0.4 kg; 95% CI, -0.8 to 0.1).</p>
<p>Arechavaleta et al.⁹⁶ (2011)</p> <p>Sitagliptin 100 mg/day</p> <p>vs</p> <p>glimepiride 1 mg/day, titrated up to 6 mg/day</p>	<p>DB, NI, RCT</p> <p>Patients with type 2 diabetes, HbA_{1c} 6.5 to 9.0%, and on a stable dose of metformin (\geq1,500 mg/day) combined with diet and exercise for \geq12 weeks</p>	<p>N=1,035</p> <p>30 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary Proportions of patients achieving HbA_{1c} <7.0%, change in baseline FPG, hypoglycemia, body weight</p>	<p>Primary: After 30 weeks, the least squares mean change in HbA_{1c} from baseline was -0.47% with sitagliptin compared to -0.54% with glimepiride, with a between-group difference of 0.07% (95% CI, -0.03 to 0.16). This result met the prespecified criterion for declaring non-inferiority.</p> <p>Secondary: The proportions of patients with HbA_{1c} <7.0% at week 30 were 52 and 60% with sitagliptin and glimepiride, respectively.</p> <p>The least squares mean change in FPG from baseline was -0.8 mmol/L (95% CI, -1.0 to -0.6) with sitagliptin compared to -1.0 mmol/L (95% CI, -1.2 to -0.8) with glimepiride, for a between-group difference of 0.2 mmol/L (95% CI, -0.1 to 0.4).</p> <p>The proportions of patients who reported hypoglycemia were 7 and 22% with sitagliptin and glimepiride (percentage-point difference, -15; P<0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Relative to baseline, sitagliptin was associated with a mean weight loss compared to a mean weight gain with glimepiride (-0.8 vs 1.2 kg), yielding a between-group difference of -2.0 kg ($P<0.001$).
Srivastava et al. ⁹⁷ (2012) Sitagliptin 50 mg/day, titrated up to 100 mg/day vs glimepiride 1 mg/day, titrated up to 2 mg/day	PG, RCT Patients with type 2 diabetes inadequately controlled with metformin alone	N=50 18 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG and two-hour PPG, body weight, hypoglycemia	Primary: At 18 weeks, both treatments significantly ($P<0.001$) reduced baseline HbA _{1c} (-0.636 vs -1.172%), with 12% of patients receiving sitagliptin and 36% of patients receiving glimepiride achieving target HbA _{1c} . Secondary: Reductions were significant ($P<0.001$) for both treatments in FPG (-15.49 vs -26.84 mg, respectively) and two-hour PPG (-34.28 vs -44.83 mg, respectively). Sitagliptin showed a net decrease in body weight by 0.102 kg, whereas glimepiride showed net increase in body weight by 0.493 kg. Incidence of hypoglycemia was 4 and 8% with sitagliptin and glimepiride.
Seck et al. ⁹⁸ (2011) Sitagliptin vs glimepiride	DB, RCT Patients with type 2 diabetes receiving metformin	N=803 1 year	Primary: Composite endpoint of HbA _{1c} reduction, lack of hypoglycemia, and no body weight Secondary: Not reported	Primary: Both treatments provided similar degrees of glycemic efficacy (least squares mean difference, -0.67%; between-group difference, -0.01; 95% CI, -0.09 to 0.08); however, significantly more patients receiving sitagliptin achieved an HbA _{1c} reduction >0.5% without hypoglycemia and without an increase in body weight (least squares mean difference, -1.5 vs 1.1 kg; $P<0.001$; between-group difference, -2.5 kg; 95% CI, -3.1 to -2.0). Patients receiving glimepiride reported more than 10 times as many events of hypoglycemia compared to patients receiving sitagliptin. Secondary: Not reported
Charbonnel et al. ⁹⁹ (2013) Sitagliptin starting at 100 mg/day, with glimepiride added if further	AC, OL, RCT Patients with type 2 diabetes mellitus aged 18 to 79 years, on a stable dose of metformin	N=653 (per protocol patients were analyzed, N=522) 26 weeks	Primary: Change in HbA _{1c} (non-inferiority) Secondary: FPG, plasma lipids, safety	Primary: HbA _{1c} decreased over 26 weeks in both treatment strategy groups, with a larger initial reduction at week 12 in the injectable group. The mean change in HbA _{1c} at week 26 was -1.3% in the oral group and -1.4% in the injectable group. The primary hypothesis was met to declare that the oral treatment was non-inferior to the injectable in lowering HbA _{1c} .

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>glucose control needed (oral)</p> <p>vs</p> <p>liraglutide starting at 0.6 mg/day, up-titrated to 1.2 mg/day after 1 week (injectable)</p>	<p>monotherapy $\geq 1,500$ mg/day for ≥ 12 weeks, with an $HbA_{1c} \geq 7.0\%$ and $\leq 11.0\%$ and a fasting fingerstick glucose < 15 mmol/L at the randomization visit, deemed capable by the investigator of using a Victoza pen injection device</p>			<p>Secondary: Significant reductions in FPG at week 26 were observed in both groups, with a greater reduction observed in the injectable group. No meaningful between-group differences were found in any lipid variable or in the incidence of clinical adverse effects overall. The incidence of drug-related adverse events or adverse events leading to discontinuation was greater in the injectable group than in the oral group. These differences were mainly related to the significantly higher incidence of gastrointestinal adverse events, such as abdominal pain, diarrhea, nausea, and vomiting, in the injectable group.</p>
<p>Takahata et al.¹⁰⁰ (2013)</p> <p>Sitagliptin 50 mg/day</p> <p>vs</p> <p>pioglitazone 15 mg/day</p> <p>(both groups could have doses titrated up at 16 weeks if $HbA_{1c} \geq 6.5\%$)</p>	<p>MC, OL, RCT</p> <p>Japanese type 2 diabetic men and women between the ages of 20 and 75 years whose diabetes had been inadequately controlled (HbA_{1c}, 6.9 to 9.5%) with metformin and/or sulfonylurea.</p>	<p>N=130</p> <p>Up to 24 weeks</p>	<p>Primary: Difference in the mean changes in the HbA_{1c} level from baseline at 24 weeks</p> <p>Secondary: Levels of FPG, fasting insulin, inflammation mediators, N-terminal pro-B-type natriuretic peptide, and markers of lipids, uric acid, liver function, and renal function</p>	<p>Primary: Difference in HbA_{1c} in the sitagliptin group was -0.86 and in the pioglitazone group was -0.58 ($P=0.024$).</p> <p>Secondary: Difference in FPG and fasting insulin did not differ significantly between groups. Body weight decreased by 0.29 kg in the sitagliptin group and increased by 1.70 kg in the pioglitazone group ($P<0.001$). The levels of LDL-C and HDL-C were significantly decreased in the sitagliptin group. The triglyceride level was not altered. The Estimated glomerular filtration rate and creatinine level were significantly exacerbated in both groups, and the uric acid level was also exacerbated in the sitagliptin group.</p> <p>Hypoglycemia (3.4 vs 3.5%), gastrointestinal symptoms (5.2 vs 1.8%) and pedal edema (0 vs 68.4%, $P<0.001$) were observed for 24 weeks in the sitagliptin and pioglitazone groups, respectively. No severe cases of hypoglycemia, rash, or bone fracture were observed in either group during the trial.</p>
<p>Perez-Monteverde et al.¹⁰¹ (2011)</p> <p>Sitagliptin 100 mg</p>	<p>DB, RCT</p> <p>Patients with type 2 diabetes and HbA_{1c} 7.5 to 12.0%</p>	<p>N=492 (Phase 1)</p> <p>12 weeks (Phase 1) plus</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary:</p>	<p>Primary: At the end of Phase 1 (12 weeks), mean changes from baseline in HbA_{1c} were -1.0 and -0.9% with sitagliptin and pioglitazone. At the end of Phase 2 (40 weeks), improvements in HbA_{1c} were greater with combination therapy compared to pioglitazone (-1.7 vs -1.4%; $P=0.002$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>QD</p> <p>vs</p> <p>sitagliptin/ metformin</p> <p>vs</p> <p>pioglitazone 30 to 45 mg QD</p> <p>In Phase 1, patients were randomized to either sitagliptin 100 mg QD or pioglitazone 30 mg QD. In Phase 2, patients randomized to sitagliptin in Phase 1 were switched to sitagliptin/ metformin, and patients randomized to pioglitazone in Phase 1 were up titrated to 45 mg/day</p>		<p>28 weeks (Phase 2)</p>	<p>Change in baseline FPG and 2-hour PPG, proportion of patients achieving HbA_{1c} <7.0%, safety, body weight</p>	<p>Secondary:</p> <p>At the end of Phase 1 (12 weeks), mean changes from baseline were -26.6 and -28.0 mg/dL for FPG and -52.8 and -50.1 mg/dL for 2-hour PPG. At the end of Phase 2 (40 weeks), improvements in FPG and 2-hour PPG were greater with combination therapy compared to pioglitazone (-45.8 vs -37.6 mg/dL; P=0.03 and -90.3 vs -69.1 mg/dL; P=0.001).</p> <p>Significantly more patients receiving combination therapy achieved an HbA_{1c} <7.0% (55.0 vs 40.5%; P=0.004).</p> <p>A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of edema were observed with combination therapy compared to pioglitazone. The incidence of hypoglycemia was similarly low with both treatments.</p> <p>Body weight decreased with combination therapy and increased with pioglitazone (-1.1 vs 3.4 kg; P<0.001).</p>
<p>Wainstein et al.¹⁰² (2012)</p> <p>Sitagliptin/ metformin 50/500 mg BID, titrated</p>	<p>DB, RCT</p> <p>Treatment-naïve patients with type 2 diabetes HbA_{1c} 7.5 to 12.0%</p>	<p>N=517</p> <p>32 weeks</p>	<p>Primary:</p> <p>Change from baseline HbA_{1c}, proportion of patients who achieved HbA_{1c}</p>	<p>Primary:</p> <p>The least squares mean changes in HbA_{1c} at week 32 were -1.9 and -1.4% with combination therapy compared to pioglitazone, respectively (between-group differences, -0.5%; P<0.001).</p> <p>A greater proportion of patients achieved an HbA_{1c} <7.0% at week 32 with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>up to 50/1,000 mg BID</p> <p>vs</p> <p>pioglitazone 30 mg/day, titrated up to 45 mg/day</p>			<p><7.0%</p> <p>Secondary: Change from baseline FPG</p>	<p>combination therapy compared to pioglitazone (57 vs 43%; P<0.001).</p> <p>Secondary: Compared to pioglitazone, combination therapy resulted in a greater least squares mean reductions in FPG (-56.0 vs -44.0 mg/dL; P<0.001) and 2-hour PPG (-102.2 vs -82.0 mg/dL; P<0.001) at week 32. A substantially greater reduction in FPG (-40.5 vs -13.0 mg/dL; P<0.001) was observed at week 1 with combination therapy compared to pioglitazone.</p> <p>A greater reduction in the fasting proinsulin:insulin and a greater increased in HOMA-B were observed with combination therapy compared to pioglitazone, while greater decreases in fasting insulin and HOMA-IR, and a greater increase in quantitative insulin sensitivity check index were observed with pioglitazone compared to combination therapy.</p> <p>Combination therapy resulted in a decrease in body weight (-1.4 kg) and pioglitazone resulted in an increase in body weight (3.0 kg; P<0.001).</p> <p>Higher incidences of diarrhea (15.3 vs 4.3%; P<0.001), nausea (4.6 vs 1.2%; P=0.02), and vomiting (1.9 vs 0.0%; P=0.026), and a lower incidence of edema (1.1 vs 7.0%; P<0.001) were observed with combination therapy compared to pioglitazone.</p> <p>There was no difference between the two treatments in the incidence of hypoglycemia (8.4 vs 8.3%; P=0.055).</p>
<p>Scott et al.¹⁰³ (2008)</p> <p>Sitagliptin 100 mg QD plus metformin (existing therapy)</p> <p>vs</p> <p>rosiglitazone 8 mg QD plus</p>	<p>AC, DB, MC, PG, RCT</p> <p>Type 2 diabetics 18 to 75 years of age receiving stable metformin doses ($\geq 1,500$ mg/day for ≥ 10 weeks) and inadequate glycemic control ($HbA_{1c} \geq 7.0$ and $\leq 11.0\%$)</p>	<p>N=273</p> <p>18 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, β cell function, insulin resistance, and lipid profile</p>	<p>Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.50%; 95% CI, -0.87 to -0.60; P\leq0.001). Similar results were observed with rosiglitazone (treatment difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). There was no difference between sitagliptin and rosiglitazone (treatment difference, -0.06%; 95% CI, -0.25 to 0.14).</p> <p>The proportion of patients achieving an HbA_{1c}<7.0% was significantly greater with sitagliptin (55%; P=0.006) and rosiglitazone (63%; P value not reported) compared to placebo (38%). There was no difference between sitagliptin and rosiglitazone (treatment difference, 8%; 95% CI, -</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>metformin (existing therapy)</p> <p>vs</p> <p>metformin (existing therapy) plus placebo</p>				<p>6 to 22; P value not reported).</p> <p>Secondary: Sitagliptin (treatment difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; $P \leq 0.001$) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo.</p> <p>Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported).</p> <p>Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; $P \leq 0.05$) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported).</p> <p>Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported).</p> <p>Rosiglitazone significantly decreased fasting serum insulin compared to placebo (treatment difference, -3.4 μIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 μIU/mL; 95% CI, -5.50 to -1.40; P value not reported).</p> <p>The proinsulin:insulin ratio was similar across all treatments.</p> <p>Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				11.8 to -0.9; $P \leq 0.05$) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin (treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; $P \leq 0.05$) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported).
Derosa et al. ¹⁰⁴ (2010) Sitagliptin 100 mg QD vs metformin 850 mg BID All patients were receiving pioglitazone (15 or 30 mg/day).	DB, RCT Patients with type 2 diabetes, HbA _{1c} >7.5%, and receiving pioglitazone 30 mg/day	N=151 12 months	Primary: Body weight, BMI, HbA _{1c} , FPG, PPG, fasting plasma insulin, HOMA-IR, HOMA-B, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, adiponectin, resistin, TNF- α , high sensitivity CRP Secondary: Not reported	Primary: A decrease in body weight and BMI were observed in patients receiving metformin, which was not observed in patients receiving sitagliptin. Significant decreases in HbA _{1c} , FPG, and PPG, and significant increases in HOMA-B were comparable between the two treatment groups. Fasting plasma insulin, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, and HOMA-IR were decreased with both treatments. While values were lower with metformin, there were no significant differences observed between the two treatments. Sitagliptin achieved no significant changes in changes in adiponectin, resistin, TNF- α , compared to a significant increase in adiponectin and significant decreases in resistin and TNF- α achieved with metformin. High sensitivity CRP decreased significantly with both treatments, with no difference between them. Secondary: Not reported
Rigby et al. ¹⁰⁵ (2010) Sitagliptin 100 mg QD and metformin (existing therapy) vs	OL Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control (HbA _{1c} 6.5	N=169 16 weeks	Primary: Change in HbA _{1c} from baseline to week 16 Secondary: Change in HbA _{1c} from baseline to	Primary: At week 16, HbA _{1c} was reduced from baseline in all treatment groups (least square mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; $P=0.031$); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; $P<0.001$); sitagliptin -0.4% (95% CI, -0.64 to -0.13; $P=0.009$). Secondary: At week eight, HbA _{1c} was reduced from baseline with colesevelam and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy)</p> <p>vs</p> <p>colesevelam 3.75 g daily (QD or BID) and metformin (existing therapy)</p>	<p>to 10.0% on a stable regimen of metformin (1,500 to 2,550 mg daily), with LDL-C \geq60 mg/dL and TG <500 mg/dL</p>		<p>week eight, change in FPG and fasting insulin from baseline to weeks eight and 16, change in two-hour PPG and postprandial insulin after a meal tolerance test, change in lipid parameters, percentage of participants who achieved an HbA_{1c} reduction >0.7% from baseline, percentage of participants who achieved HbA_{1c} <7.0%</p>	<p>sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109).</p> <p>FPG was significantly reduced from baseline at week eight and week 16 in all treatment groups.</p> <p>The two-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups.</p> <p>There was no significant change in fasting insulin or two-hour postprandial insulin from baseline to week 16 in any treatment group.</p> <p>Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008).</p> <p>LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011).</p> <p>TC levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median triglyceride levels increased significantly from baseline with colesevelam (P<0.001) and rosiglitazone (P<0.001); however, sitagliptin did not significantly affect TG levels. HDL-C levels did not change significantly from baseline with any treatment.</p> <p>At week 16, 23.2% of patients in the colesevelam group, 48.1 % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in HbA_{1c} 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved HbA_{1c} <7.0%.</p> <p>The percentages of patients who had an adverse event were 61.4% in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in severity.
VilSBøll et al. ¹⁰⁶ (2010) Sitagliptin 100 mg QD vs placebo All patients received insulin therapy with or without metformin.	RCT, DB, PC, PG Patients ≥21 years of age with type 2 diabetes on insulin (≥15 IU/day) alone or in combination with metformin (≥1500 mg/day) who had inadequate glycemic control (HbA _{1c} 7.5 to 11%), and BMI 20 to 43 kg/m ²	N=641 24 weeks	Primary: Change in HbA _{1c} from baseline Secondary: FPG, two-hour postmeal glucose, and the proportion of patients with an HbA _{1c} <7.0% or <6.5% at week 24	Primary: At week 24, the addition of sitagliptin to insulin therapy (± metformin) significantly reduced HbA _{1c} by 0.6% (P<0.001) compared with no change in the placebo group. Secondary: At week 24, mean change in FPG from baseline was -18.5 mg/dL in the sitagliptin group compared to -3.5 mg/dL in the placebo group (P<0.001). The two-hour post meal glucose was significantly reduced from baseline in the sitagliptin group (-30.9 mg/dL) compared to placebo (+5.2 mg/dL; P<0.001). The proportion of patients with an HbA _{1c} <7.0% at week 24 was significantly higher in the sitagliptin group compared with the placebo group (13 vs 5%, respectively). There was no difference between groups in the proportion of patients with an HbA _{1c} <6.5% at week 24.
Esposito et al. ¹⁰⁷ (2011) Alogliptin 12.5 to 25 mg QD vs saxagliptin 5 mg QD vs sitagliptin 100 mg QD vs	MA (43 RCT) Type 2 diabetics were treatment-naïve or receiving background therapy with other agents	N=19,101 Duration not reported	Primary: Proportion of patients achieving an HbA _{1c} <7.0%, change in baseline body weight, incidence of hypoglycemia Secondary: Not reported	Primary: Proportion of patients achieving an aHbA _{1c} <7.0% Treatment with saxagliptin demonstrated a greater chance to achieve n HbA _{1c} <7.0% compared to placebo (POR, 2.81; 95% CI, 2.31 to 3.72), but not compared to comparator drugs (POR, 0.95; 95% CI, 0.8 to 1.11). Saxagliptin was associated with a greater decrease in HbA _{1c} compared to placebo (WMD, -0.69%; 95% CI, -0.1 to -0.37), but not compared to comparator drugs (WMD, 0.15%; 95% CI, -0.14 to 1.7). Sitagliptin was associated with a greater chance to achieve an HbA _{1c} <7.0% compared to placebo (POR, 3.15; 95% CI, 2.47 to 3.72), but not compared to comparator drugs (POR, 0.70; 95% CI, 0.35 to 1.12). Sitagliptin was also associated with a greater decrease in HbA _{1c} compared to placebo (WMD, -0.78%; 95% CI, -0.93 to -0.63), but not compared to comparator drugs (WMD, 0.19%; 95% CI, -0.13 to 0.52). Change in baseline body weight

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vildagliptin* 100 mg QD				<p>Saxagliptin was associated with small and no significant changes in body weight compared to baseline or other comparator drugs (WMD, -0.56 kg; 95% CI, -2.8 to 1.7), but with a significant difference compared to placebo (0.63 kg; 95% CI, 0.03 to 1.17).</p> <p>The absolute change in weight was small and not significantly different from baseline with sitagliptin (0.08 kg); however, the difference compared to placebo was significant (WMD, 0.48 kg; 95% CI, 0.19 to 0.77). The overall change in weight with sitagliptin was not different from that of comparator drugs.</p> <p>Incidence of hypoglycemia Saxagliptin was associated with similar risk of hypoglycemia compared to placebo (RR, 1.1; 95% CI, 0.81 to 1.42) and comparator drugs (RR, 0.55; 95% CI, 0.4 to 1.9).</p> <p>Sitagliptin was associated with a significantly lower risk of hypoglycemia compared to placebo (RR, 1.8; 95% CI, 0.61 to 2.5) and comparator drugs (RR, 0.87; 95% CI, 0.30 to 2.80).</p> <p>Secondary: Not reported</p>
Park et al. ¹⁰⁸ (2012) Sitagliptin vs saxagliptin vs vildagliptin* vs	MA Patients ≥ 18 years of age with type 2 diabetes	N=30,563 (62 RCTs) 12 or more weeks	Primary: Mean changes in HbA _{1c} and body weight, safety Secondary: Not reported	Primary: DPP-4 inhibitors lowered HbA _{1c} significantly more than placebo (weighted mean difference [WMD] -0.76%; 95% CI, -0.83 to -0.68); however, heterogeneity was substantial (I ² =82%). Exclusion of Japanese trials (N=7) resulted in a reduction of heterogeneity (I ² =59%). In the non-Japanese RCTs (N=55), DPP-4 inhibitors were associated with a reduction in HbA _{1c} (WMD -0.65%; 95% CI, -0.71 to -0.60) but higher risk of hypoglycemia (OR, 1.30; 95% CI, 1.00 to 1.68) compared to placebo. The seven Japanese-specific RCTs showed a greater reduction in HbA _{1c} (WMD -1.67%; 95% CI, -1.89 to -1.44) and a nonsignificant increase in risk of hypoglycemia (OR, 1.41; 95% CI, 0.51 to 3.88) with DPP-4 inhibitors vs placebo. When comparing DPP-4 inhibitors to active comparators, the I ² was still high after deleting Japanese studies. In these 17 active comparator trials, there was no significant difference in HbA _{1c} reduction (WMD 0.04%; 95% CI, -0.09 to 0.16) or risk of hypoglycemia

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
linagliptin				<p>(OR, 0.60; 95% CI, 0.22 to 1.61) for DPP-4 inhibitors compared to other antihyperglycemics. There were similar odds of any or serious adverse events with DPP-4 inhibitors compared to placebo, but a decreased risk compared to other antihyperglycemics.</p> <p>Secondary: Not reported</p>
<p>Mearns et al.¹⁰⁹ (2015)</p> <p>Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)</p>	<p>Network MA (62 RCTs)</p> <p>Patients with inadequately controlled type 2 diabetes on metformin alone</p>	<p>N=32,185</p> <p>3 to 12 months</p>	<p>Primary: Changes in HbA_{1c}, body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection</p> <p>Secondary: Not reported</p>	<p>Primary: All agents significantly reduced HbA_{1c} vs placebo; although, not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03).</p> <p>Secondary: Not reported</p>
<p>Kheirbek et al.¹¹⁰ (2013)</p> <p>Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide,</p>	<p>OS, RETRO</p> <p>Veterans with diabetes cared for at a Veterans Administration Capital area medical center</p>	<p>N=17,773</p> <p>Variable duration</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Not reported</p>	<p>Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use				statistically significant increased mortality after controlling for possible drug interactions. Secondary: Not reported

*Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous

Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-dummy, ES=extension study, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, SA=single-arm, SR=systematic review, XO=cross-over

Miscellaneous: AUC=area under the curve, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein-cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein-cholesterol, MI=myocardial infarction, OR=odds ratio, PGWB=Psychological General Well-being index, PPG=post-prandial glucose, POR=pooled odds ratio, QOL=quality of life, QUICKI=Quantitative insulin sensitivity check index, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TNF- α =tumor necrosis factor- α , TZD=thiazolidinedione, ULN=upper limit of normal, WMD=weighted mean difference

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 10. Relative Cost of the Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Alogliptin	tablet	Nesina ^{®*}	\$\$\$\$\$	\$\$\$\$
Linagliptin	tablet	Tradjenta [®]	\$\$\$\$\$	N/A
Saxagliptin	tablet	Onglyza [®]	\$\$\$\$\$	N/A
Sitagliptin	tablet	Januvia [®]	\$\$\$\$\$	N/A
Combination Products				
Alogliptin and metformin	tablet	Kazano ^{®**}	\$\$\$\$\$	\$\$\$\$
Alogliptin and pioglitazone	tablet	Oseni ^{®**}	\$\$\$\$\$	\$\$\$\$
Linagliptin and metformin	tablet	Jentaduetto [®] , Jentaduetto XR [®]	\$\$\$\$\$	N/A
Saxagliptin and metformin	extended-release tablet	Kombiglyze XR [®]	\$\$\$\$\$	N/A
Sitagliptin and metformin	extended-release, tablet, tablet	Janumet [®] , Janumet XR [®]	\$\$\$\$\$	N/A

N/A=Not available

X. Conclusions

The dipeptidyl peptidase-4 (DPP-4) inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Available DPP-4 inhibitor combination products with metformin and pioglitazone are available for use when treatment with both drug components is appropriate.¹⁻¹¹

Alogliptin and alogliptin combination products are available in a generic formulation; metformin and pioglitazone are also available generically in a separate formulation.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The DPP-4 inhibitors are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin as advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents. Patients who are not appropriate for initial therapy with metformin may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, an SGLT2 inhibitor, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one DPP-4 inhibitor over another is not stated.¹²⁻²⁴

A variety of clinical trials have been conducted with the DPP-4 inhibitors. The majority of the clinical trials have compared active treatment to placebo in patients not adequately controlled on other antidiabetic medications. In these trials, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.²⁷⁻¹¹⁰ In treatment naïve patients, sitagliptin was shown to be non-inferior to metformin when used as monotherapy; however, monotherapy with exenatide was more beneficial with regards to glycemic parameters compared to monotherapy with sitagliptin.³⁹⁻⁴⁰ Sitagliptin was also shown to be as effective as rosiglitazone or glipizide when these agents were added to existing metformin monotherapy.^{94,103} The addition of exenatide to metformin led to a greater reduction in two-hour postprandial glucose concentrations compared to the addition of sitagliptin to metformin.³⁸ Limited head-to-head clinical trials comparing DPP-4 inhibitors have been conducted. In one trial, saxagliptin demonstrated non-inferiority to sitagliptin when both agents were added to existing metformin therapy.⁷⁸ There have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.⁵⁻¹² Available trials evaluating the fixed-dose combination of sitagliptin and metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.⁸⁹ Alogliptin and pioglitazone combination therapy has also demonstrated significant improvements in HbA_{1c} when compared to monotherapy with either agent.⁵³⁻⁵⁵ According to current type 2 diabetes guidelines, DPP-4 inhibitors may be considered as a second-line therapy in addition to metformin when blood glucose control is inadequate.¹²⁻²⁰

The DPP-4 inhibitors are generally well tolerated. There have been postmarketing reports of serious hypersensitivity reactions in patients taking a DPP-4 inhibitor. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. There have also been reports in the postmarketing setting and in randomized clinical trials of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking a DPP-4 inhibitor. Additional warnings and precautions include heart failure, hepatic effects, severe arthralgia, and bullous pemphigoid. In the EXAMINE trial which enrolled patients with type 2 diabetes and recent acute coronary syndrome, 106 (3.9%) of patients treated with alogliptin and 89 (3.3%) of patients treated with placebo were hospitalized for congestive heart failure. Consider the risks and benefits of alogliptin prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy.^{4,50} Combination DPP-4 inhibitor products containing metformin are associated with a risk of lactic acidosis.¹⁻¹¹

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the DPP-4 inhibitors or any other antidiabetic drug.¹⁻¹¹

There is insufficient evidence to support that one brand DPP-4 inhibitor is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand DPP-4 inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Tradjenta[®] [package insert]. Ridgefield (CT) and Indianapolis (IN): Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company; 2016 Dec.
2. Onglyza[®] [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals LP; 2017 Jan.
3. Januvia[®] [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2017 Jan.
4. Nesina[®] [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2016 Dec.
5. Janumet[®] [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2017 Jan.
6. Janumet XR[®] [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2017 Jan.
7. Jentadueto[®] [package insert]. Ridgefield (CT) and Indianapolis (IN): Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company; 2016 Dec.
8. Jentadueto XR[®] [package insert]. Ridgefield (CT) and Indianapolis (IN): Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company; 2016 Dec.
9. Kombiglyze XR[®] [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals LP; 2017 Jan.
10. Kazano[®] [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2017 Feb.
11. Oseni[®] [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2016 Dec.
12. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* 2016;39(Suppl. 1):S1–S112.
13. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012 Jun;35(6):1364-79.
14. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2015 Mar;58(3):429-42.
15. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2012 Feb 7;156(3):218-31.
16. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract*. 2015 Apr;21 Suppl 1:1-87.
17. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. *Endocr Pract*. 2016;22(1):84-113..
18. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
19. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
20. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
21. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. *Pediatrics* 2013;131(2):364-382.
22. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.
23. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.
24. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. *Diabetes Care* 2014;37(7):2034-2054.
25. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Feb]. Available from: <http://www.thomsonhc.com/>.

26. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Feb 2017]. Available from: <http://online.factsandcomparisons.com>.
27. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 010 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2008 Dec;31(12):2315-7.
28. Rosenstock J, Sankoh S, List J. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naïve patients with type 2 diabetes. *Diabetes Obes Metab* 2008;10:376-386.
29. Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes (abstract). *Curr Med Res Opin*. 2009;25:2401-2411.
30. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013 Oct 3;369(14):1317-26. doi: 10.1056/NEJMoa1307684.
31. Aschner P, Kipnes MS, Luncford JK, Sanchez M, Mickel C, Williams-Herman DE; Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2006 Dec;29(12):2632-7.
32. Hanefeld M, Herman GA, Wu M, Mickel C, Sanchez M. Once-daily sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatment of patients with type 2 diabetes. *Curr Med Res Opin*. 2007 Apr 30; [Epub ahead of print].
33. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H; Sitagliptin Study 023 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia*. 2006 Nov;49:2564-71.
34. Nonaka K, Kakikawa T, Sato A, Okuyama K, Fujimoto G, Kato N, Suzuki H, Hirayama Y, Ahmed T, Davies MJ, Stein PP. Efficacy and safety of sitagliptin monotherapy in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2007 Oct 12; [Epub ahead of print].
35. Hartley P, Shentu Y, Betz-Schiff P, et al. Efficacy and Tolerability of Sitagliptin Compared with Glimepiride in Elderly Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control: A Randomized, Double-Blind, Non-Inferiority Trial. *Drugs Aging*. 2015 Jun;32(6):469-76.
36. Scott R, Wu M, Sanchez M, Stein P. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. *Int J Clin Pract*. 2007 Jan;61(1):171-80.
37. Chan J, Scott R, Arjona Ferreira J, et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. *Diabetes Obes Metab* 2008;10:545-555.
38. DeFronzo R, Okerson T, Viswanathan P, et al. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. *Curr Med Res Opin* 2008;24:2943-2952.
39. Aschner P, Katzeff HL, Guo H, et al. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. *Diabetes Obes Metab* 2010;12:252-61.
40. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzolez JG, Chan M, et al. Efficacy and safety of exenatide once weekly vs metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4). *Diabetes Care*. 2012;35:252-8.
41. Monami M, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin* 2011;27 Suppl 3:57-64.
42. Fakhoury WKH, LeReun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. *Pharmacology*. 2010;86(1):44-57.
43. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes. *JAMA*. 2007 Jul;298(2):194-206.
44. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD006423. DOI: 10.1002/14651858.CD006423.pub2.
45. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared to exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. *Ann Pharmacother*. 2011;45:850-60.
46. Nauck MA, Ellis GC, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 008 Group. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. *Int J Clin Pract*. 2009 Jan;63(1):46-55.

47. Pratley RE, Reusch JE, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 009 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Curr Med Res Opin.* 2009 Oct;25(10):2361-71.
48. Pratley RE, Kipnes MS, Fleck PR, Wilson C, Mekki Q; Alogliptin Study 007 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. *Diabetes Obes Metab.* 2009 Feb;11(2):167-76.
49. Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia. *Diabetes Obes Metab.* 2009 Dec;11(12):1145-52.
50. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet.* 2015 May 23;385(9982):2067-76.
51. Rosenstock J, Wilson C, and Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. *Diabetes, Obesity and Metabolism* 2013;15(10):906–914.
52. Del Prato S, Camisasca R, Wilson C, Fleck P. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. *Diabetes Obes Metab.* 2014 Dec;16(12):1239-46.
53. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naïve patients with type 2 diabetes. *Diabetes Care.* 2010 Nov;33(11):2406-8.
54. DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2012 May;97(5):1615-22.
55. Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. *Diabetes Obes Metab.* 2011 Dec;13(12):1088-96.
56. Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. *Diabetes Care.* 2014 Oct;37(10):2723-30.
57. Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptin monotherapy on glycemic control and markers of β -cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. *Diabetes Obes Metab.* 2011;13:258-67.
58. Taskinen MR, Rosenstock J, Tamminen I, Kubiak R, Patel S, Dugi KA, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2011;13:65-74.
59. Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. *Diabet Med.* 2011;28:1352-61.
60. Bajaj M, Gilman R, Patel S, Kempthorne-Rawson J, Lewis-D'Agostino D, Woerle HJ. Linagliptin improved glycaemic control without weight gain or hypoglycaemia in patients with type 2 diabetes inadequately controlled by a combination of metformin and pioglitazone: a 24-week randomized, double-blind study. *Diabet Med.* 2014 Dec;31(12):1505-14.
61. Forst T, Uhlig-Laske B, Ring A, Graefe-Mody U, Friedrich C, Herbach K, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled type 2 diabetes. *Diabet Med.* 2010;27:1409-19.
62. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin improves glycemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2012;14:565-74.
63. Haak T, Meinicke T, Jones R, et al. Initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomised, double-blind 1-year extension study. *Int J Clin Pract* 2013;67(12):1283–1293.
64. Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2011;13:653-61.
65. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care.* 2015 Mar;38(3):376-83.

66. Chacra AR, Tan GH, Apanovitch A, et al. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. *Int J Clin Pract* 2009;63:1395-406.
67. Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin*. 2012 Apr;28(4):513-23.
68. Stenlöf K, Raz I, Neutel J, Ravichandran S, Berglind N, Chen R. Saxagliptin and metformin XR combination therapy provides glycemic control over 24 hours in patients with T2DM inadequately controlled with metformin. *Curr Med Res Opin*. 2010 Oct;26(10):2355-63.
69. Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin*. 2012 Apr;28(4):513-23.
70. Matthaai S, Catrinou D, Celiński A, et al. Randomized, Double-Blind Trial of Triple Therapy With Saxagliptin Add-on to Dapagliflozin Plus Metformin in Patients With Type 2 Diabetes. *Diabetes Care*. 2015 Nov;38(11):2018-24.
71. Scherthaner G, Durán-García S, Hanefeld M, et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). *Diabetes Obes Metab*. 2015 Jul;17(7):630-8.
72. Hermans MP, Delibasi T, Farmer I, et al. Effects of saxagliptin added to sub-maximal doses of metformin compared with uptitration of metformin in type 2 diabetes: the PROMPT study. *Current Medical Research & Opinion* 2012;28(10):1635-1645.
73. DeFronzo R, Hissa M, Garber A, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care* 2009;32:1649-1655.
74. Pfützner A, Paz-Pacheco E, Allen E, Frederich R, Chen R; CV181039 Investigators. Initial combination therapy with saxagliptin and metformin provides sustained glycemic control and is well tolerated for up to 76 weeks. *Diabetes Obes Metab*. 2011 Jun;13(6):567-76.
75. Jadzinsky M, Pfützner A, Paz-Pacheco E, et al. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes Obes Metab* 2009;11:611-22.
76. Hollander P, Li J, Allen E, Chen R. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. *J Clin Endocrinol Metab* 2009;94:4810-4819.
77. Frederich R, Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. *Postgrad Med*. 2010 May;122(3):16-27.
78. Scheen AJ, Charpentier G, Ostgren CJ, Hellqvist A, Gause-Nilsson I. Efficacy and safety of saxagliptin in combination with metformin compared to sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. *Diabetes Metab Res Rev*. 2010 Oct;26(7):540-9.
79. Göke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I; D1680C00001 Investigators. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. *Int J Clin Pract*. 2010 Nov;64(12):1619-31.
80. Göke B, Gallwitz B, Eriksson JG, et al. Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. *Int J Clin Pract* 2013; 67(4):307–316. doi: 10.1111/ijcp.12119
81. Harashima SI, Ogura M, Tanaka D, Fukushima T, Wang Y, Koizumi T, et al. Sitagliptin add-on to low dosage sulphonylureas: efficacy and safety of combination therapy on glycemic control and insulin secretion capacity in type 2 diabetes. *Int J Clin Pract*. 2012 May;66(5):465-76.
82. Brazg R, Xu L, Dalla Man C, Cobelli C, Thomas K, Stein PP. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and beta-cell function in patients with type 2 diabetes. *Diabetes Obes Metab*. 2007 Mar;9(2):186-93.
83. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care*. 2006 Dec;29(12):2638-43.
84. Derosa G, Ragonesi PD, Fogari E, et al. Sitagliptin added to previously taken antidiabetic agents on insulin resistance and lipid profile: a 2-year study evaluation. *Fundamental & Clinical Pharmacology* 2014;28:221–229.

85. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015 Jul 16;373(3):232-42.
86. Raz I, Chen Y, Wu M, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. *Curr Med Res Opin* 2008;24:537-550.
87. Derosa G, Carbone A, Franzetti I, et al. Effects of a combination of sitagliptin plus metformin vs metformin monotherapy on glycemic control, β -cell function and insulin resistance in type 2 diabetic patients. *Diabetes Research and Clinical Practice* 2012;98:51-60.
88. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE Sitagliptin 036 Study Group. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2007 Aug;30(8):1979-87.
89. Reasner C, Olansky L, Seck TL, Williams-Herman DE, Terranella L, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared to metformin monotherapy in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2011 Jul;13(7):644-52.
90. Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P; Sitagliptin Study 019 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther*. 2006 Oct;28(10):1556-68.
91. Lavallo-González FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 2013; 56:2582–2592.
92. Weinstock RS, Guerci B, Umpierrez G, Nauck MA, Skrivaneck Z, Milicevic Z. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. *Diabetes Obes Metab*. 2015 Sep;17(9):849-58.
93. Bergenstal RM, Wysham C, MacConell L, Malloy J, Walsh B, Yan P, et al. Efficacy and safety of exenatide once weekly vs sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomized trial. *Lancet*. 2010;376:431-9.
94. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP; Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab*. 2007 Mar;9(2):194-205.
95. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab*. 2007 Sep;9(5):733-45.
96. Arechavaleta R, Seck T, Chen Y, KJ Krobot, EA O'Neill, L Duran, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes, Obesity and Metabolism*. 2011;13:160-8.
97. Srivastava A, Saxena GN, Keshwani P, Gupta R. Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone. *JAPI*. 2012 Mar;60:27-30.
98. Seck TL, Engel SS, Williams-Herman DE, Sisk CM, Golm GT, Wang H, et al. Sitagliptin more effectively achieves a composite endpoint for A1C reduction, lack of hypoglycemia and no body weight gain compared with glipizide. *Diabetes Research and Clinical Practice*. 2011;93:e15-7.
99. Charbonnel B, Steinberg H, Eymard E, et al. Efficacy and safety over 26 weeks of an oral treatment strategy including sitagliptin compared with an injectable treatment strategy with liraglutide in patients with type 2 diabetes mellitus inadequately controlled on metformin: a randomised clinical trial. *Diabetologia* 2013; 56:1503–1511.
100. Takihata M, Nakamura A, Tajima K, et al. Comparative study of sitagliptin with pioglitazone in Japanese type 2 diabetic patients: the COMPASS randomized controlled trial. *Diabetes, Obesity and Metabolism* 2011;15(5):455–462.
101. Perez-Monteverde A, Seck T, Xu L, Lee MA, Sisk CM, Williams-Herman DE, et al. Efficacy and safety of sitagliptin and fixed-dose combination of sitagliptin and metformin vs pioglitazone in drug-naïve patients with type 2 diabetes. *Int J Clin Pract*. 2011 Sep;65(9):930-8.
102. Wainstein J, Katz L, Engel SS, Xu L, Golm GT, Hussain S, et al. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with

- pioglitazone monotherapy in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism*. 2012;14:409-18.
103. Scott R, Loeys T, Davies M, Engel S. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2008;10:959-969.
 104. Derosa G, Maffioli P, Salvadeo SAT, Ferrari I, Ragonesi PD, Querci F, et al. Effects of sitagliptin or metformin added to pioglitazone monotherapy in poorly controlled type 2 diabetes mellitus patients. *Metabolism Clinical and Experimental*. 2010;59:887-95.
 105. Rigby SP, Handelsman Y, Lai YL, et al. Effects of colesevelam, rosiglitazone, or sitagliptin on glycemic control and lipid profile in patients with type 2 diabetes mellitus inadequately controlled by metformin monotherapy. *Endocr Pract* 2010;16:53-63.
 106. Vilsbøll T, Rosenstock J, Yki-Järvinen H, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2010;12:167-77.
 107. Esposito K, Cozzolino D, Bellastella G, Maiorino MI, Chiodini P, Ceriello A, et al. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2011 Jul;13(7):594-603.
 108. Park H, Park C, Kim Y, and Rascati KL. Efficacy and Safety of Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes: Meta-Analysis. *The Annals of Pharmacotherapy* 2012; 46:1453-1469.
 109. Mearns ES, Sobieraj DM, White CM, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One*. 2015 Apr 28;10(4):e0125879.
 110. Kheirbek RE, Alemi F, Zargoush M. Comparative effectiveness of hypoglycemic medications among veterans. *J Manag Care Pharm*. 2013;19(9):740-44.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Incretin Mimetics
AHFS Class 682006
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The incretin mimetics are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹⁻⁷ The incretin mimetics are glucagon-like peptide-1 (GLP-1) receptor agonists. GLP-1 is a human incretin hormone that is secreted from the small intestine in response to food intake, which has multiple effects on the stomach, liver, pancreas and brain to control glucose concentrations. Human GLP-1 is inactivated by the dipeptidyl peptidase-4 (DPP4) enzyme within minutes. Endogenous GLP-1 levels have been shown to be reduced in patients with type 2 diabetes. Exenatide is a synthetic peptide with approximately 50% homology to human GLP-1, but is more resistant to inactivation by DPP-4. Liraglutide is an acylated human GLP-1 with 97% homology to the endogenous form and also has increased stability against metabolic degradation. Albiglutide is a recombinant fusion protein that has been modified to confer resistance to DPP-4 proteolysis, thereby lengthening the half life to five days and allowing for once weekly dosing. **Dulaglutide is 90% homologous to native human GLP-1 and is dosed weekly.** The incretin mimetics enhance glucose-dependent insulin secretion by pancreatic beta cells, suppress glucagon secretion, slow gastric emptying, and reduce food intake.¹⁻⁷

The incretin mimetics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available. This class was last reviewed in February 2015.

Table 1. Incretin Mimetics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Albiglutide	injection	Tanzeum®	none
Dulaglutide	injection	Trulicity®	none
Exenatide	injection	Byetta®, Bydureon®	none
Liraglutide	injection	Victoza®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Incretin Mimetics

Clinical Guideline	Recommendation(s)
American Diabetes Association: Standards of Medical Care in Diabetes (2016)⁸	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) \geq6.5%, or a fasting plasma glucose (FPG) \geq126 mg/dL, or a two-hour plasma glucose \geq200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose \geq200 mg/dL).

Clinical Guideline	Recommendation(s)
	<p><u>Prevention or delay of type 2 diabetes</u></p> <ul style="list-style-type: none"> • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥ 150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. • Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus. • Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p><u>Glycemic goals in adults</u></p> <ul style="list-style-type: none"> • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is $<7.0\%$. • It may be reasonable for providers to suggest more stringent HbA_{1c} goals ($<6.5\%$) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals ($<8.0\%$) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p><u>Pharmacologic therapy for type 1 diabetes</u></p> <ul style="list-style-type: none"> • Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. • Most patients should use of insulin analogs to reduce hypoglycemia risk. • Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. <p><u>Pharmacologic therapy for type 2 diabetes</u></p> <ul style="list-style-type: none"> • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If the A_{1c} target is not achieved after approximately three months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with

Clinical Guideline	Recommendation(s)
	<p>type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed.</p> <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • <u>Pregestational Diabetes</u> <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1C} <6.5%, to reduce the risk of congenital anomalies. ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. • <u>Gestational Diabetes Mellitus</u> <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. • <u>General Principles for Management of Diabetes in Pregnancy</u> <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. • Due to increased red blood cell turnover, A_{1C} is lower in normal pregnancy than in normal nonpregnant women. The A_{1C} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: <u>Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012 and 2015 Update)</u>^{9,10}</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> • Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. • Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. • In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. • Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Clinical Guideline	Recommendation(s)						
	Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations						
Initial Drug Monotherapy	Metformin						
Efficacy (↓HbA _{1c})	High						
Hypoglycemia	Low risk						
Weight	Neutral/loss						
Side Effects	Gastrointestinal/lactic acidosis						
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)							
Two Drug Combinations	Metformin + sulfonyl-urea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)	
Efficacy (↓HbA _{1c})	High	High	Inter-mediate	Inter-mediate	High	Highest	
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk	
Weight	Gain	Gain	Neutral	Loss	Loss	Gain	
Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia	
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)							
Three Drug Combinations	Metformin + sulfonyl-urea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + TZD + Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + DPP-4 inhibitor + Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin	Metformin + SGLT2 inhibitor + Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin	Metformin + GLP-1 receptor agonist + Sulfonyl-urea, TZD, or insulin	Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist	
If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents							
More Complex Insulin Strategies	Combination injectable therapy						
American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012) ¹¹	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. 						
American Association of Clinical Endocrinologists/ American College Of Endocrinology: Clinical Practice Guidelines for Developing a Diabetes Mellitus	<p>Antihyperglycemic pharmacotherapy for type 2 diabetes</p> <ul style="list-style-type: none"> The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement. Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. Antihyperglycemic agents may be broadly categorized by whether they 						

Clinical Guideline	Recommendation(s)
<p>Comprehensive Care Plan (2015)¹²</p>	<p>predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.</p> <ul style="list-style-type: none"> • Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. • When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. • The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. • When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists: Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm 2016 (2016)¹³</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} \leq6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be

Clinical Guideline	Recommendation(s)
	<p>given to monitoring requirements and risks of hypoglycemia and weight gain.</p> <ul style="list-style-type: none"> • The therapeutic regimen should be as simple as possible to optimize adherence. <p>Monotherapy</p> <ul style="list-style-type: none"> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ Sodium glucose cotransporter 2 (SGLT-2) inhibitors. ○ DPP-4 inhibitors. ○ . ○ TZDs (use with caution). ○ Alpha-glucosidase inhibitors. • sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p>Combination therapy</p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ DPP-4 inhibitors. ○ TZD. ○ Basal insulin. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p>Three-drug combination therapy</p> <ul style="list-style-type: none"> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Insulin therapy algorithm</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <p><u>Basal insulin</u></p> <ul style="list-style-type: none"> • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p><u>Basal-bolus insulin regimens</u></p> <ul style="list-style-type: none"> • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. <p><u>Basal insulin and incretin therapy regimens</u></p> <ul style="list-style-type: none"> • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and

Clinical Guideline	Recommendation(s)
	<p>postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.</p>
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last updated July 2016)¹⁴</p>	<p>Individualized care</p> <ul style="list-style-type: none"> • Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective. • Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p>HbA_{1c} targets</p> <ul style="list-style-type: none"> • Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. • For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. • In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> ○ reinforce advice about diet, lifestyle and adherence to drug treatment and ○ support the person to aim for an HbA_{1c} level of 7.0% and ○ intensify drug treatment. • Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> ○ who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy ○ for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job ○ for whom intensive management would not be appropriate, for example, people with significant comorbidities. • If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p>Drug treatment</p> <ul style="list-style-type: none"> • For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost • If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. • Initial drug treatment

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m²: <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p>First intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. • Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes. <p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment. • If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with

Clinical Guideline	Recommendation(s)
	<p>type 2 diabetes who:</p> <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. <ul style="list-style-type: none"> ● Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in six months). ● In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment. ● In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. ● Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p><u>Insulin-based treatments</u></p> <ul style="list-style-type: none"> ● When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional. ● When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. ● Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation. ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: <ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals. ○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes: <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. • Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). • Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)¹⁵</p>	<ul style="list-style-type: none"> • Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. • Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical Guidelines Task Force:</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> • Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes.

Clinical Guideline	Recommendation(s)
<p>Global Guideline for Type 2 Diabetes (2012)¹⁶</p>	<ul style="list-style-type: none"> • Match the timing of medication (including insulin) and meals. • Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. • Introduce physical activity gradually, based on the individual’s willingness and ability, and setting individualized and specific goals. • Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. • Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> • Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. • A lower HbA_{1c} target may be considered if it is easily and safely achieved. • A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> • Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. • Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. • First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. • Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. • Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering

Clinical Guideline	Recommendation(s)
	<p>mediations (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control.</p> <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)¹⁷</p>	<ul style="list-style-type: none"> • Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations ≥ 250 mg/dL. ○ Whose HbA_{1c} is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
<p>National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November</p>	<p><u>Education and information for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control

Clinical Guideline	Recommendation(s)
<p>2016¹⁸</p>	<ul style="list-style-type: none"> ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. • Tailor the education programme to each child or young person with type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. • Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Encourage children and young people with type 1 diabetes to wear or carry something that identifies them as having type 1 diabetes (e.g., a bracelet). • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. • Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations. • Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p><u>Insulin therapy for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. • Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen. • Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. • Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. • Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. • Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin infusion users. • Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. • Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin (0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%. • Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. • Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. • Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with type 1 diabetes a review of injection sites at each clinic visit. • Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. • If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily

Clinical Guideline	Recommendation(s)
	<p>injections, continuous subcutaneous insulin infusion [CSII or insulin pump] therapy or once-, twice- or three-times daily mixed insulin injections).</p> <p><u>Oral medicines for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. <p><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. • Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. • Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. • Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain. <p><u>Education and information for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ HbA_{1c} monitoring and targets ○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control ○ the aims of metformin therapy and possible adverse effects ○ the complications of type 2 diabetes and how to prevent them. • Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every 2 years. • Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes

Clinical Guideline	Recommendation(s)
	<p>support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards.</p> <ul style="list-style-type: none"> • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. <p><u>Dietary management for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. • Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. • At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. • Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications. • Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. • Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. • At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI. • Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. • Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy. <p><u>Metformin</u></p> <ul style="list-style-type: none"> • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management (Published 2015; last updated July 2016)¹⁹</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> • Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. • Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target. • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ total glycated hemoglobin estimation (if abnormal hemoglobins). ● Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. ● Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia. ● Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p>Self-monitoring of blood glucose</p> <ul style="list-style-type: none"> ● Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least four times a day, including before each meal and before bed. ● Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). ● Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia. ● Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. ● Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy) ● Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking. <p>Continuous glucose monitoring</p> <ul style="list-style-type: none"> ● Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. ● Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause. ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level ≥9%) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in

Clinical Guideline	Recommendation(s)
	<p data-bbox="656 205 911 233">HbA_{1c} of 2.5% or more.</p> <ul data-bbox="513 237 1395 359" style="list-style-type: none"> <li data-bbox="513 237 1395 359">• For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. <p data-bbox="513 390 695 417">Insulin regimens</p> <ul data-bbox="513 422 1386 604" style="list-style-type: none"> <li data-bbox="513 422 1386 543">• Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. <li data-bbox="513 548 1386 604">• Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only). <p data-bbox="513 636 727 663">Long-acting insulin</p> <ul data-bbox="513 667 1406 1005" style="list-style-type: none"> <li data-bbox="513 667 1406 724">• Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. <li data-bbox="513 728 1406 911">• Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul data-bbox="607 764 1406 911" style="list-style-type: none"> <li data-bbox="607 764 1406 821">○ an existing insulin regimen being used by the person that is achieving their agreed targets <li data-bbox="607 825 1406 911">○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. <li data-bbox="513 915 1406 1005">• Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p data-bbox="513 1037 732 1064">Rapid-acting insulin</p> <ul data-bbox="513 1068 1414 1283" style="list-style-type: none"> <li data-bbox="513 1068 1414 1159">• Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. <li data-bbox="513 1163 1414 1220">• Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. <li data-bbox="513 1224 1414 1283">• If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. <p data-bbox="513 1314 667 1341">Mixed insulin</p> <ul data-bbox="513 1346 1411 1535" style="list-style-type: none"> <li data-bbox="513 1346 1411 1436">• Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. <li data-bbox="513 1440 1411 1535">• Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p data-bbox="513 1566 802 1593">Optimizing insulin therapy</p> <ul data-bbox="513 1598 1406 1898" style="list-style-type: none"> <li data-bbox="513 1598 1406 1898">• For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously optimized insulin regimen, the following should be considered: <ul data-bbox="607 1688 1406 1898" style="list-style-type: none"> <li data-bbox="607 1688 1406 1715">○ injection technique <li data-bbox="607 1719 1406 1747">○ injection sites <li data-bbox="607 1751 1406 1778">○ self-monitoring skills <li data-bbox="607 1782 1406 1810">○ knowledge and self-management skills <li data-bbox="607 1814 1406 1841">○ nature of lifestyle <li data-bbox="607 1845 1406 1873">○ psychological and psychosocial difficulties <li data-bbox="607 1877 1406 1898">○ possible organic causes such as gastroparesis.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. <p><u>Adjuncts</u></p> <ul style="list-style-type: none"> • Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> • Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. • Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. • Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. • After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. • Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. • Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. • Check injection site condition at least annually and if new problems with blood glucose control occur.
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)²⁰</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> • Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. • If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <p><u>Glycemic control goals</u></p> <ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p> <ul style="list-style-type: none"> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the incretin mimetics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

It is important to note that the incretin mimetics are not a substitute for insulin, and these agents should not be used in type 1 diabetics or for the treatment of diabetic ketoacidosis. The incretin mimetics would not be effective in these situations.¹⁻⁵

According to FDA-approved package labeling, due to the uncertain relevance of the rat thyroid C-cell tumor findings to humans, albiglutide, dulaglutide, exenatide (Bydureon®), and liraglutide are not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.²⁻⁵

Table 3. FDA-Approved Indications for the Incretin Mimetics¹⁻⁵

Generic Name	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus
Albiglutide	✓
Dulaglutide	✓
Exenatide	✓
Liraglutide	✓

IV. Pharmacokinetics

The pharmacokinetic parameters of the incretin mimetics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Incretin Mimetics⁶

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Albiglutide	Not reported	Not reported	Vascular endothelium (% not reported)	Not reported	120
Dulaglutide	47 to 65	Not reported	Protein catabolism (% not reported)	Not reported	120
Exenatide	65 to 76†	Not reported	Plasma/tissues (% not reported)	Renal (% not reported)	2.4
Liraglutide	55	>98	Not significant (% not reported)	Renal (0 unchanged; 6 changed), Feces (0 unchanged; 5 unchanged)	13

†Information derived from animal data.

V. Drug Interactions

There are no significant drug interactions reported with the incretin mimetics.⁷ However, these agents slow gastric emptying and thereby have the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with the incretin mimetics.¹⁻⁵

VI. Adverse Drug Events

The most common adverse drug events reported with the incretin mimetics are listed in Table 5. The boxed warning for the incretin mimetics are listed in Tables 6 through 9. Based on postmarketing data, the incretin mimetics have been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Patients may develop antibodies to exenatide consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. In a small percentage of patients, the

formation of antibodies to exenatide at high titers could result in failure to achieve adequate improvement in glycemic control.¹⁻⁵

Table 5. Adverse Drug Events (%) Reported with the Incretin Mimetics⁷

Adverse Event	Albiglutide	Dulaglutide	Exenatide/ Exenatide Extended-Release	Liraglutide
Abdominal distention	-	2 to 3	-	-
Abdominal pain	-	7 to 9	-	-
Anorexia	-	-	-	9
Antibody development (non-neutralizing)	6	2	-	-
Arthralgia	7	-	-	-
Asthenia	-	-	4	-
Atrioventricular block	-	2	-	-
Atrial fibrillation	1	-	-	-
Back pain	7	-	-	5
Constipation	-	4	-6.3 to 10.1	5.1 to 9.9
Cough	7	-	-	-
Decreased appetite	-	5 to 9	1 to 2/5	9.3
Diarrhea	13	9 to 13	1 to 13/9.3 to 20.0	7.2 to 17.1
Dizziness	-	-	1 to 9	5.2
Dyspepsia	-	4 to 6	3 to 7/5.0 to 7.4	5.2 to 6.5
Eructation	-	1 to 2	-	-
Fatigue	-	4 to 6	-5.6 to 6.1	5.1
Feeling jittery	-	-	9	-
Flatulence	-	3	-	-
Gastroenteritis viral	-	-	-8.8	-
Gastroesophageal reflux disease	4	2	3/7.4	-
Headache	-	-	9/6.1 to 9.9	8.2 to 9.6
Hyperhidrosis	-	-	3	-
Hypertension	-	-	-	3
Hypoglycemia	3 to 17	3 to 6	3.8 to 35.7/0 to 20	0.1 to 27.4
Increased Gamma-Glutamyl Transferase	2	-	-	-
Influenza	5	-	-	7.4
Injection site erythema	2	-	-5.4 to 7.4	-
Injection site hematoma	-	-	-5.4	-
Injection site nodule	-	-	-6.0 to 10.5	-
Injection site pruritus	-	-	-5.0 to 18.2	-
Injection site reaction	11 to 18	-	-	-
Nasopharyngitis	-	-	-	5.2
Nausea	11	12 to 21	8 to 44/11.3 to 27.0	7.5 to 34.6
Pneumonia	2	-	-	-
P-R prolongation	-	3	-	-
Sinus tachycardia	-	3 to 6	-	-
Sinusitis	-	-	-	5.6
Upper respiratory tract infection	14	-	-	9.5
Urinary tract infection	-	-	-	6
Vomiting	4	6 to 13	4 to 13/10.8 to 11.3	6.5 to 12.4

*Corresponds to monotherapy or combination therapy with other antidiabetic therapies.

-Event not reported.

Table 6. Boxed Warning for Tanzeum® (albiglutide)⁴

WARNING
<p>WARNING: RISK OF THYROID C-CELL TUMORS</p> <ul style="list-style-type: none"> • Carcinogenicity of albiglutide could not be assessed in rodents, but other glucagon-like peptide-1 (GLP-1) receptor agonists have caused thyroid C-cell tumors in rodents at clinically relevant exposures. Human relevance of GLP-1 receptor agonist induced C-cell tumors in rodents has not been determined. It is unknown whether Tanzeum® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. • Tanzeum is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with the use of Tanzeum and inform them of the symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound monitoring is of uncertain value for early detection of MTC in patients treated with Tanzeum.

Table 7. Boxed Warning for Trulicity® (dulaglutide)⁵

WARNING
<p>WARNING: RISK OF THYROID C-CELL TUMORS</p> <ul style="list-style-type: none"> • In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined. • Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with use of Trulicity and inform them of symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Trulicity.

Table 8. Boxed Warning for Bydureon® (exenatide extended-release)²

WARNING
<p>WARNING: RISK OF THYROID C-CELL TUMORS</p> <ul style="list-style-type: none"> • Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether Bydureon causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined. • Bydureon is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Bydureon and inform them of symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for detection of MTC in patients treated with Bydureon.

Table 9. Boxed Warning for Victoza® (liraglutide)³

WARNING
<p>WARNING: RISK OF THYROID C-CELL TUMORS</p> <ul style="list-style-type: none"> • Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. • Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Victoza and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Victoza.

VII. Dosing and Administration

The usual dosing regimens for the incretin mimetics are listed in Table 10. The incretin mimetics are administered by subcutaneous injection. There are currently two formulations of exenatide available. The immediate-release formulation (Byetta[®]) is administered twice daily and should be given within 60 minutes prior to a meal, while the extended-release (ER) formulation (Bydureon[®]) is administered once weekly and can be administered without regard to meals.^{1,2} The extended effect of exenatide ER results from the addition of a biodegradable polymer poly D, L-lactic-co-glycolic acid to the active component, exenatide, which forms microspheres. After exenatide ER is administered, continued infiltration of water into the microspheres causes them to swell and release the medication in a slow predictable fashion. Of note, patients who administer exenatide ER will have a palpable SC nodule at the injection site that dissipates as the medication is released.²¹

Table 10. Usual Dosing Regimens for the Incretin Mimetics¹⁻⁵

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Albiglutide	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Injection: 30 mg SC once weekly, may be increased to 50 mg once weekly if the glycemic response is inadequate	Safety and efficacy have not been established in pediatric patients.	Injection: 30 mg/0.5 mL 50 mg/0.5 mL
Dulaglutide	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Injection: initial, 0.75 mg once weekly, may be increased to 1.5 mg once weekly	Safety and efficacy have not been established in pediatric patients.	Injection: 0.75 mg/0.5 mL 1.5 mg/0.5 mL
Exenatide	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Injection (Bydureon [®]): initial, 2 mg SC once weekly Injection (Byetta [®]): initial, 5 µg SC BID; maintenance, 10 µg SC BID after one month of therapy	Safety and efficacy have not been established in pediatric patients.	Injection: 5 µg/0.02 mL (Byetta [®])* 10 µg /0.04 mL (Byetta [®])† 2 mg/vial (Bydureon)‡ 2 mg/pen (Bydureon)^
Liraglutide	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Injection: initial, 0.6 mg SC QD for one week; maintenance, 1.2 to 1.8 mg SC QD	Safety and efficacy have not been established in pediatric patients.	Injection: 6 mg/mL§

BID=twice daily, QD=once daily, SC=subcutaneous

*Supplied as a pre-filled syringe (1.2 mL, 60 doses).

†Supplied as a pre-filled syringe (2.4 mL, 60 doses).

‡Supplied in cartons of four single-dose trays (one vial containing 2 mg exenatide, one pre-filled syringe, one vial connector, and two custom needles).

^Supplied in cartons of four single-dose pens containing 2 mg of exenatide and diluent and including one needle. Each carton contains one spare needle.

§Supplied as 0.6 (30 doses), 1.2 (15 doses), and 1.8 mg (10 doses) pre-filled, multi-dose pens (3 mL) available in a package of two or three pens.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the incretin mimetics are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Incretin Mimetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
<p>Nauck et al.²² (2016) HARMONY 2</p> <p>Albiglutide 30 mg or 50 mg once weekly</p> <p>vs</p> <p>placebo</p>	<p>PC, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes uncontrolled by diet and exercise (HbA_{1c} ≥7.0 and ≤10.0%)</p>	<p>N=309</p> <p>3 years</p>	<p>Primary: Change in HbA_{1c} from baseline to week 52</p> <p>Secondary: FPG, proportions of patients achieving HbA_{1c} values ≤6.5 and ≤7.0%, weight, safety</p>	<p>Primary: Over 52 weeks of treatment, HbA_{1c} decreased from baseline in both albiglutide groups and increased in the placebo group. The treatment difference (albiglutide minus placebo) of the model-adjusted least-squares mean change in HbA_{1c} from baseline to week 52 was statistically significant for both albiglutide groups (albiglutide 30 mg: -0.84%; 95% CI, -1.11 to -0.58%; P<0.0001; albiglutide 50 mg: -1.04%; 95% CI, -1.31 to -0.77%; P<0.0001).</p> <p>Secondary: Changes in FPG at week 52 were consistent with HbA_{1c} results. The treatment difference was statistically significant for both albiglutide groups (albiglutide 30 mg vs placebo: -1.89 mmol/l; 95% CI, -2.55 to -1.22; P<0.0001; albiglutide 50 mg vs placebo: -2.38 mmol/l; 95% CI, -3.05 to -1.71; P<0.0001). At week 52, the HbA_{1c} treatment goal of <7.0% was met by 49.0, 40.2, and 21.4% of patients treated with albiglutide 30 mg, albiglutide 50 mg and placebo, respectively (both P≤0.0002) and the goal of HbA_{1c} <6.5% was met by 25.0, 24.7, and 10.2% of patients treated with albiglutide 30 mg, albiglutide 50 mg and placebo, respectively (both P<0.005). The difference in the time to hyperglycaemia rescue was statistically significant in favour of each albiglutide group (albiglutide 30 mg or 50 mg; P<0.0001).</p> <p>Weight loss was not statistically significantly different when comparing the placebo and albiglutide groups at week 52 (least-squares mean change from baseline -0.39 kg with albiglutide 30 mg, -0.86 kg with albiglutide 50 mg and -0.66 kg with placebo). For the safety profile at week 52, the proportion of patients experiencing adverse events was higher with albiglutide 30 mg and albiglutide 50 mg than with placebo.</p>
<p>Miyagawa et al.²³ (2015)</p>	<p>DB, PC, OL, RCT (blinded to treatment)</p>	<p>N=492</p> <p>52 weeks</p>	<p>Primary: Comparison of change in HbA_{1c}</p>	<p>Primary: At 26 weeks, once-weekly dulaglutide was superior to placebo for HbA_{1c} change from baseline (P<0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Dulaglutide subcutaneous 0.75 mg once-weekly</p> <p>vs</p> <p>Liraglutide subcutaneous injections uptitrated from 0.3 mg/day during week 1 to 0.6 mg/day during week 2 and 0.9 mg/day starting at week 3</p> <p>vs</p> <p>placebo</p>	<p>assignment for dulaglutide and placebo but not for liraglutide)</p> <p>Patients with type 2 diabetes ≥ 20 years of age who were oral antidiabetic medication-naïve (diet and exercise only) or had discontinued oral antidiabetic medication monotherapy (excluding thiazolidinedione).</p>		<p>from baseline at 26 weeks in dulaglutide vs placebo superiority</p> <p>Secondary: Comparison of change in HbA_{1c} from baseline at 26 weeks in dulaglutide vs liraglutide non-inferiority</p>	<p>Secondary: Dulaglutide was non-inferior, but not superior, to once-daily liraglutide ($P_{\text{non-inferiority}} < 0.001$).</p> <p>The LS mean (standard error) changes in HbA_{1c} from baseline to 26 weeks were -1.43% (0.05) for dulaglutide, -1.33% (0.07) for liraglutide, and 0.14% (0.10) for placebo. The LS mean difference between dulaglutide and placebo was -1.57% (95% CI, -1.79 to -1.35) and between dulaglutide and liraglutide was -0.10% (95% CI, -0.27 to 0.07). For each timepoint from baseline to primary endpoint, dulaglutide significantly reduced HbA_{1c} compared with placebo ($P < 0.001$ all timepoints).</p>
<p>Moretto et al.²⁴ (2008)</p> <p>Exenatide 5 μg BID</p> <p>vs</p> <p>exenatide 10 μg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, PG, RCT</p> <p>Patients ≥ 18 years of age with type 2 diabetes who were drug naïve and whose diabetes was inadequately controlled on diet and exercise alone</p>	<p>N=232</p> <p>24 weeks</p>	<p>Primary: HbA_{1c}, fasting serum glucose, six-point self-monitored blood glucose, proportions of patients achieving HbA_{1c} values ≤ 6.5 and $\leq 7.0\%$, weight; HOMA-B, safety</p> <p>Secondary: Not reported</p>	<p>Primary: Mean changes in HbA_{1c} from baseline (LSM) were significantly greater with exenatide 5 and 10 μg compared to placebo (-0.7 and -0.9 vs -0.2%, respectively; $P=0.003$ and $P<0.001$ vs placebo).</p> <p>Mean changes in fasting serum glucose from baseline were significantly greater with exenatide 5 and 10 μg compared to placebo (-17.5 and -18.7 vs -5.2 mg/dL, respectively; $P=0.029$ and $P=0.016$ vs placebo).</p> <p>Changes in daily mean PPG excursions from baseline to end point were significantly greater with exenatide 5 and 10 μg compared to placebo (-21.3 and -24.7 vs -8.3 mg/dL, respectively; $P<0.001$ vs placebo for both).</p> <p>With exenatide 5 and 10 μg, 31 and 35% of patients achieved HbA_{1c} $\leq 6.5\%$ at end point vs 19% of patients receiving placebo (P value not significant and $P=0.026$, respectively), while 48 and 46 vs 29% of patients achieved HbA_{1c} $\leq 7.0\%$ ($P=0.024$ and $P=0.036$, respectively).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Changes in weight at 24 weeks were greater with exenatide 5 and 10 µg compared to placebo (-2.8 and -3.1 vs -1.4 kg, respectively; P=0.004 and P<0.001).</p> <p>HOMA-B values increased from baseline to end point by 32 and 28% with exenatide 5 and 10 µg, respectively, compared to 6% with placebo. Improvements from baseline to end point in HOMA-B were significantly greater with exenatide 5 and 10 µg compared to placebo (P=0.002 and P=0.010, respectively).</p> <p>Significant improvements in mean SBP and DBP from baseline to end point were also observed with exenatide (SBP: exenatide 5 and 10 µg, -3.7 mm Hg; P=0.037, DBP: exenatide 10 µg, -2.3 mm Hg; P=0.046) compared to placebo (SBP: -0.3 mm Hg and DBP: -0.3 mm Hg).</p> <p>Overall, 25% of patients reported at least one treatment-emergent adverse event. Nausea was reported with the greatest incidence (exenatide 5 µg, 3%; exenatide 10 µg, 13%; placebo, 0%; P=0.010 for the combined exenatide group vs placebo). Most (88%) treatment-emergent adverse events were mild or moderate in intensity.</p> <p>Hypoglycemia was reported in five, four, and one percent of patients receiving exenatide 5 and 10 µg and placebo groups, respectively (P value not significant), with no incidents of severe hypoglycemia reported.</p>
<p>DeFronzo et al.²⁵ (2008)</p> <p>Exenatide 5 µg BID for 1 week, then 10 µg BID for 1 week</p> <p>vs</p> <p>sitagliptin 100 mg QD for 2 weeks</p>	<p>DB, MC, RCT, XO</p> <p>Patients 18 to 70 years of age with type 2 diabetes who were treated with a stable regimen of metformin, HbA_{1c} 7.0 to 11.0%, FPG <280 mg/dL, and BMI 25 to 45 kg/m²</p>	<p>N=95</p> <p>4 weeks</p>	<p>Primary: 2-hour PPG</p> <p>Secondary: Postprandial insulin, glucagon, active GLP-1 and TG concentrations, and safety</p>	<p>Primary: The 2-hour PPG concentration (LSM) was lower for exenatide compared to sitagliptin (133 vs 208 mg/dL; P<0.0001). In the ITT population, the 2-hour PPG concentration was lower with exenatide compared to sitagliptin (166 vs 210 mg/dL, respectively; P<0.0001).</p> <p>The change in 2-hour PPG concentration (least square mean) from baseline was -112 mg/dL for exenatide compared to -37 mg/dL for sitagliptin (P<0.0001).</p> <p>FPG was similar following treatment with exenatide (-15 mg/dL) and sitagliptin (-19 mg/dL; P=0.3234).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>All patients were receiving existing metformin regimens.</p>				<p>Following crossover to the alternate therapy, patients switched from exenatide to sitagliptin experienced an increase in mean 2-hour PPG +73 mg/dL. Patients switched from sitagliptin to exenatide treatment experienced a reduction in the mean 2-hour PPG concentration -76 mg/dL.</p> <p>Secondary: The acute insulin response was greater for exenatide compared to sitagliptin (P=0.0017).</p> <p>Both exenatide and sitagliptin reduced the mean postprandial plasma glucagon concentration compared to baseline; however, the reduction was greater with exenatide compared to sitagliptin (P=0.0011).</p> <p>Both exenatide and sitagliptin both reduced mean postprandial TG concentrations compared to baseline; however, the decrease was greater with exenatide compared to sitagliptin (P=0.0118).</p> <p>Exenatide reduced the rate of gastric emptying compared to baseline and to sitagliptin (P<0.0001). Sitagliptin had no effect on gastric emptying).</p> <p>Adverse events with exenatide and sitagliptin were mild-to-moderate. The most common adverse events were gastrointestinal with both treatments. Nausea was experienced by 34% of patients treated with exenatide and 12% of patients treated with sitagliptin. Vomiting was experienced by 24% of patients treated with exenatide and 3% of patients treated with sitagliptin. No serious treatment-emergent adverse events were reported during the study.</p>
<p>Bergental et al.²⁶ (2009)</p> <p>Exenatide 5 µg BID for 4 weeks, then 10 µg BID</p> <p>vs</p> <p>insulin aspart 12 units QD before dinner (BIAsp 30</p>	<p>OL, PG, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes mellitus and HbA_{1c} ≥8%, insulin-naïve, and receiving treatment with metformin and a sulfonylurea for at least 3 months prior</p>	<p>N=372</p> <p>24 Weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: FPG, eight-point plasma glucose profiles, changes in body weight</p>	<p>Primary: At 24 weeks, HbA_{1c} values were 7.61, 7.75, 8.46% for BIAsp 30 BID, BIAsp 30 QD, and exenatide, respectively (both P<0.0001 compared to exenatide).</p> <p>At the end of the study, 37% of patients in the BIAsp 30 BID group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group (P=0.0060). Additionally, 25% of patients in the BIAsp 30 BID group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.0004).</p> <p>At the end of the study, 26% of patients in the BIAsp 30 QD group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>QD)</p> <p>vs</p> <p>insulin aspart 12 units divided equally before breakfast and dinner (BIAsp 30 BID)</p> <p>All patients were receiving metformin with or without a sulfonylurea.</p> <p>Insulin dose was titrated as necessary.</p>	<p>to enrolling in the study</p>			<p>(P=0.3488). Additionally, 12% of patients in the BIAsp 30 QD group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.3802).</p> <p>The percentage of patients who achieved HbA_{1c} ≤6.5% was higher with BIAsp 30 BID compared to BIAsp 30 QD (25 vs 12%; P=0.0122).</p> <p>Secondary: There were significant changes in FPG with BIAsp 30 BID (-62.7 mg/dL; P<0.0001 vs exenatide) and BIAsp 30 QD (-52.4 mg/dl; P=0.0002 vs exenatide) compared to exenatide (-21.4 mg/dL).</p> <p>At the end of the study, the eight-point plasma glucose profiles were significantly lower with BIAsp 30 BID and BIAsp 30 QD than exenatide.</p> <p>At 24 weeks, hypoglycemia was reported in 56% of patients in the BIAsp 30 QD group, 61% of patients in the BIAsp 30 BID group, and 29% in the exenatide group.</p> <p>Weight loss was reported in the exenatide group (-1.9 kg) compared with weight gain in the BIAsp 30 QD (+2.8 kg) and BIAsp 30 BID (4.1 kg).</p> <p>There were more reports of nausea and vomiting with exenatide than in the insulin groups.</p>
<p>Xu et al.²⁷ (2015) CONFIDENCE</p> <p>Exenatide twice daily</p> <p>vs</p> <p>insulin (75% insulin lispro protamine suspension and 25% insulin lispro</p>	<p>MC, PG, RCT</p> <p>Treatment-naïve patients 30 to 70 years of age with newly diagnosed type 2 diabetes</p>	<p>N=416</p> <p>48 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Effects on weight, blood pressure, lipid profiles and β-cell function</p>	<p>Primary: At week 48, mean HbA_{1c} changes from baseline were -1.8% (95% CI, -1.55 to -2.05%) with exenatide, -1.7% (95% CI, -1.52 to -1.96%) with insulin and -1.5% (95% CI, -1.23 to -1.71%) with pioglitazone. Treatment differences were -0.20% (95% CI, -0.46 to 0.06%) for exenatide vs insulin (P=0.185), and -0.37% (95% CI, -0.63 to -0.12%) for exenatide vs pioglitazone (P=0.002).</p> <p>Secondary: Mean weight change was significantly different between the exenatide group and the insulin and pioglitazone groups from weeks four and eight until the end of the study, with weight decreasing in the exenatide group. Decreases in mean systolic and diastolic blood pressures at 48 weeks were not statistically different between groups, although significant decreases in systolic and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>injection) twice daily</p> <p>vs</p> <p>pioglitazone once daily</p>				<p>diastolic blood pressures were observed with exenatide ($P < 0.05$ vs baseline), and a significant decrease in diastolic blood pressure alone was found with pioglitazone ($P < 0.001$). Exenatide treatment resulted in improvements in overall lipid profiles, with significant decreases in TG, total cholesterol and LDL cholesterol levels, and an increase in HDL cholesterol ($P < 0.05$ vs baseline for all variables). HDL cholesterol increased with pioglitazone ($P < 0.001$), and LDL cholesterol decreased with insulin ($P < 0.05$).</p> <p>At week 48, HOMA-B (which, together with fasting proinsulin-to-insulin ratio (PI/I), provides an indication of β-cell function during the fasting state) increased in patients treated with insulin ($P < 0.001$ vs baseline). Improvements from baseline were similar in all treatment groups with regard to PI/I, as well as acute insulin response (AIR, which represents β-cell function during the stimulated state after intravenous glucose injection). Disposition index (DI), which provides a measure of β-cell function during the stimulated state under near-physiological conditions of food intake via the gastrointestinal system, increased significantly in all treatment groups ($P < 0.001$ vs baseline for exenatide; $P < 0.05$ vs baseline for insulin and pioglitazone). The greatest mean improvements from baseline in DI and AIR were observed in the exenatide treatment group.</p>
<p>Russell-Jones et al.²⁸ (2012) DURATION-4</p> <p>Exenatide ER 2 mg SC once weekly</p> <p>vs</p> <p>metformin 2,000 mg/day</p> <p>vs</p> <p>pioglitazone 45 mg/day</p>	<p>DB, DD, MC, PG, RCT</p> <p>Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m², and stable weight</p>	<p>N=820</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving HbA_{1c} <7.0 and $\leq 6.5\%$, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported</p>	<p>Primary: Decreases in HbA_{1c} were -1.53 ± 0.07, -1.48 ± 0.07, -1.63 ± 0.08, and $-1.15 \pm 0.08\%$ with exenatide ER, metformin ($P = 0.620$ vs exenatide ER), pioglitazone ($P = 0.328$ vs exenatide ER), and sitagliptin ($P < 0.001$ vs exenatide ER). The HbA_{1c} at trial end was 6.94 ± 0.07, 6.99 ± 0.07, 6.84 ± 0.08, and $7.32 \pm 0.08\%$ with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively.</p> <p>Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; $P < 0.001$), and $\leq 6.5\%$ compared to patients receiving metformin (49 vs 36%; $P = 0.004$) and sitagliptin, respectively (49 vs 26%; $P < 0.001$).</p> <p>Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin ($P < 0.001$ for both). There</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>sitagliptin 100 mg/day</p>			<p>QOL</p>	<p>were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26).</p> <p>Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments.</p> <p>Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892).</p> <p>No clinically significant changes in serum lipids were observed with any treatment.</p> <p>Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329).</p> <p>Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>All treatments resulted in improvements in perceived treatment satisfaction, weight-related QOL, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related QOL, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported).</p>
<p>Fakhoury et al.²⁹ (2010)</p> <p>Incretin-based therapies (exenatide, liraglutide, vildagliptin,* and sitagliptin)</p> <p>vs</p> <p>placebo</p>	<p>MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, vildagliptin)</p> <p>Type 2 diabetics ≥18 years of age</p>	<p>N=Not reported</p> <p>Duration varied (4 to 52 weeks)</p>	<p>Primary: Change in baseline HbA_{1c} and weight, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; P<0.001) significantly decrease HbA_{1c} compared to placebo.</p> <p>Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; P<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; P<0.0010) significantly decreased baseline HbA_{1c}. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -0.95 to -0.73; P<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant.</p> <p>There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; P<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; P<0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; P=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide.</p> <p>Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.56; 95% CI, 1.23 to 5.33; P=0.01). When adjusted for covariates, age was the only variable found to be significant (RR, 1.84; 95% CI, 1.02 to 3.34; P=0.044). Exenatide-treated patients were 140% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.40; 95% CI, 1.39 to 4.11; P=0.002). Liraglutide-treated patients were 69% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 1.69; 95% CI, 1.00 to 2.86; P=0.050).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Monami et al.³⁰ (2011)</p> <p>GLP-1 receptor agonist based therapies (albiglutide, exenatide, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)</p> <p>vs</p> <p>other classes of antidiabetic medications or placebo</p>	<p>MA</p> <p>Type 2 diabetics</p>	<p>N=10,485</p> <p>Up to 52 weeks</p>	<p>Primary: Major cardiovascular events</p> <p>Secondary: Not reported</p>	<p>Primary: GLP-1 receptor agonists are not associated with an increased risk of cardiovascular events (OR, 0.74; 95% CI, 0.50 to 1.08; P=0.12).</p> <p>Exenatide is not associated with an increased risk of cardiovascular events (OR, 0.85; 95% CI, 0.50 to 1.45; P=0.55).</p> <p>Liraglutide is not associated with an increased risk of cardiovascular events (OR, 0.69; 95% CI, 0.40 to 1.22; P=0.20).</p> <p>In PC trials, GLP-1 receptor agonists reduced the risk of cardiovascular events (OR, 0.46; 95% CI, 0.25 to 0.83; P=0.009).</p> <p>In AC trials, there was no difference between treatments in the risk of cardiovascular events (OR, 1.05; 95% CI 0.63 to 1.76; P=0.84).</p> <p>Secondary: Not reported</p>
<p>Shyangdan et al.³¹ (2011)</p> <p>GLP-1 receptor agonist based therapies (albiglutide, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)</p> <p>vs</p> <p>non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4</p>	<p>MA (RCTs)</p> <p>Type 2 diabetics ≥18 years of age</p>	<p>N=not reported</p> <p>8 to 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change</p> <p>Secondary: Health-related QOL, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function</p>	<p>Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).</p> <p>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhibitors, insulin glargine, and sulfonylureas)				<p>1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI, -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78).</p> <p>Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).</p> <p>Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).</p> <p>Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92).</p> <p>Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).</p> <p>Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).</p> <p>Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).</p> <p>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).</p> <p>Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).</p> <p>Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Secondary: Data on mortality and morbidity were not reported for any treatment.</p> <p>QOL Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.</p> <p>Data for liraglutide were not reported.</p> <p>Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).</p> <p>Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.</p> <p>BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported.</p> <p>FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).</p> <p>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P<0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported).</p> <p>PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a 6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).</p> <p>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.</p> <p>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported.</p> <p>β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.</p>
<p>Pinelli et al.³² (2011)</p> <p>GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*)</p> <p>vs</p> <p>exenatide and sitagliptin</p>	<p>MA, SR (5 RCTs)</p> <p>Adult type 2 diabetics</p>	<p>N=not reported</p> <p>Duration varied (not reported)</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, PPG, weight, BP, and lipid profile; safety</p> <p>Secondary: Not reported</p>	<p>Primary: Pooled analysis demonstrates modest decreases in HbA_{1c} favoring long-acting GLP-1 receptor agonists over exenatide (WMD, -0.47%; 95% CI, -0.69 to -0.25) and sitagliptin (WMD, -0.60%; 95% CI, -0.75 to -0.45). Long-acting GLP-1 receptor agonists were significantly more likely to achieve HbA_{1c} <7.0% compared to exenatide (OR, 2.14; 95% CI, 1.38 to 3.34) and sitagliptin (OR, 3.84; 95% CI, 2.78 to 5.31).</p> <p>Pooled analysis demonstrates significant decreases in FPG favored long-acting GLP-1 receptor agonists compared to exenatide (WMD, -18.39 mg/dL; 95% CI, -24.67 to -12.10) and sitagliptin (WMD, -20.96; 95% CI, -27.88 to -14.04).</p> <p>In one trial, exenatide achieved significantly greater decreases in PPG compared to exenatide ER (-124 vs -95 mg/dL; P=0.01). In another trial, exenatide achieved significantly greater decreases in PPG after breakfast (treatment difference, -24 mg/dL; P<0.0001) and dinner (-18 mg/dL; P=0.0005) compared to liraglutide. There was no difference between treatments after lunch. In a third trial, exenatide ER significantly decreased PPG after each meal compared to sitagliptin (P<0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Pooled analysis demonstrates significant decreases in weight with long-acting GLP-1 receptor agonists compared to sitagliptin (WMD, -1.99 kg; 95% CI, -2.69 to -1.09), but not exenatide (WMD, -0.48 kg; 95% CI, -1.11 to 0.44).</p> <p>In one trial, exenatide ER significantly decreased SBP compared to sitagliptin (treatment difference, -4 mm Hg; P=0.006), but results were not significant in the three other trials (P values not reported). One trial demonstrated sitagliptin significantly decreased DBP compared to liraglutide (-1.78 vs 0.07 mm Hg; P=0.02). Between-group differences were not significant in the other three trials (P values not reported).</p> <p>Long-acting GLP-1 receptor agonists significantly improved TC compared to other incretin-based therapy in two of four trials. Exenatide ER significantly decreased TC (-12.0 vs -3.9 mg/dL; P value not reported) and LDL-C (-5.0 vs 1.2 mg/dL) compared to exenatide. Liraglutide significantly decreased TC compared to sitagliptin (-6.60 vs -0.77 mg/dL; P=0.03). In one trial, long-acting GLP-1 receptor agonists significantly improved TG compared to incretin-based therapy (-36 with liraglutide vs -20 mg/dL with exenatide ER; P=0.05).</p> <p>No episodes of severe hypoglycemia were reported in four of the trials. In another trial, two patients receiving exenatide experienced severe hypoglycemia. Non-severe hypoglycemia occurred infrequently and in similar amounts among the treatments. The most commonly reported adverse events with long-acting GLP-1 receptor agonists were gastrointestinal-related. Compared to exenatide, the incidence of vomiting was significantly decreased with long-acting GLP-1 receptor agonists (OR, 0.55; 95% CI, 0.34 to 0.89), there was a trend towards decreased nausea (OR, 0.58; 95% CI, 0.32 to 1.06), and no difference in diarrhea (OR, 1.03; 95% CI, 0.67 to 1.58). Nausea (OR, 4.70; 95% CI, 1.81 to 12.24), vomiting (OR, 3.22; 95% CI, 1.63 to 6.36), and diarrhea (OR, 2.32; 95% CI, 1.42 to 3.81) with long-acting GLP-1 receptor agonists were increased compared to sitagliptin. Compared to exenatide, exenatide ER caused more injection site pruritus in two trials (17.6 vs 1.4%), in another trial exenatide had a similar rate of injection site reactions compared to placebo injection (10 vs 7%). Acute pancreatitis was not reported in any trial. One patient receiving liraglutide experienced mild pancreatitis after 88 days of treatment.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Monami et al. ³³ (2008) Metformin vs sulfonylureas, α -glucosidase inhibitors, TZDs, glinides, GLP-1 agonists	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA _{1c} at 16 to 36 months Secondary: Not reported	Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α -glucosidase inhibitors, and TZDs led to a reduction in HbA _{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA _{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α -glucosidase inhibitors, and between α -glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported
Type 2 Diabetes – Combination Therapy				
Pratley et al. ³⁴ (2014) HARMONY-7 Albiglutide 30 mg SC weekly; with titration to 50 mg SC weekly starting at week 6 vs liraglutide SC QD dosed as 0.6 mg in week one, 1.2 mg in week 2, and 1.8 mg thereafter Note: The study was comprised of four phases:	IN, MC, PG, OL, RCT Patients \geq 18 years with type 2 diabetes (i.e., HbA _{1c} \geq 7.0 and \leq 10.0%) uncontrolled on metformin, thiazolidinediones, sulfonylureas, or any combination of these therapies, and a BMI \geq 20 kg/m ² and <45 kg/m ²	N=841 32 weeks	Primary: Change in HbA _{1c} from baseline at week 32 for albiglutide vs liraglutide Secondary: HbA _{1c} change from baseline over time, change in FPG from baseline over time, the proportion of patients meeting HbA _{1c} treatment goals <7.0% and <6.5%, time to hyperglycemia rescue, and change in bodyweight	Primary: At week 32, HbA _{1c} had decreased significantly from baseline in both groups. The mean HbA _{1c} level (SD) among the albiglutide-treated group decreased from 8.18% (0.89) at baseline to 7.39% (1.11) at week 32; corresponding to a treatment difference of -0.79%. The mean HbA _{1c} level (SD) among the liraglutide-treated group decreased from 8.15% (0.84) at baseline to 7.18% (1.08) at week 32; corresponding to a treatment difference of -0.98%. The treatment difference for albiglutide vs liraglutide was 0.21% (95% CI, 0.08 to 0.34; P=0.0846). Since the upper bound of the 95% CI for the treatment difference exceeded the prespecified non-inferiority margin of 0.3%, the criteria for non-inferiority of albiglutide were not met. Subgroup analyses on the primary efficacy endpoint (i.e., baseline HbA _{1c} , sex, race, ethnicity, age, diabetes duration, and background oral antidiabetic drugs) were consistent with the primary endpoint for the overall population. Secondary: At week 32, HbA _{1c} had decreased significantly from baseline in both groups. The mean HbA _{1c} level (SD) among the albiglutide-treated group decreased

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>screening, 4 weeks of run-in and stabilization, 32 weeks of treatment, and 8 weeks of post-treatment follow-up.</p>			<p>from baseline</p>	<p>from 8.18% (0.89) at baseline to 7.39% (1.11) at week 32; corresponding to a treatment difference of -0.79%. The mean percent change in HbA_{1c} level (SD) among the liraglutide-treated group decreased from 8.15% (0.84) at baseline to 7.18% (1.08) at week 32; corresponding to a treatment difference of -0.98%.</p> <p>Decreases in HbA_{1c} from baseline over time were recorded through week 32 in each treatment group, beginning at week four and stabilizing by week 12.</p> <p>Changes from baseline over time in FPG were consistent with changes in HbA_{1c}. At 32 weeks, the LSM change in FPG was -1.22 mmol/L (95% CI, -1.45 to -1.00) in the albiglutide group and -1.68 mmol/L (95% CI, -1.91 to -1.46) in the liraglutide group; corresponding to a treatment difference of 0.46 (95% CI, 0.14 to 0.78; P=0.0048).</p> <p>The HbA_{1c} treatment goal of <7.0% was achieved by 42% of albiglutide-treated patients and 52% of liraglutide-treated patients (P=0.0023); while the goal of HbA_{1c} lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009).</p> <p>Hyperglycemia rescue criteria occurred in 15% of albiglutide-treated patients and 8% of liraglutide-treated patients by week 32. The difference in time to hyperglycemia rescue favored liraglutide (P=0.005) and the probability of hyperglycemia rescue was higher in albiglutide-treated patients from week 12 to week 32 (albiglutide vs liraglutide: 0.0286 vs 0.0027 at week 12; 0.1333 vs 0.0783 at week 26; and 0.1929 vs 0.1247 at week 32).</p> <p>A significantly greater weight loss was observed in patients treated with liraglutide (-2.19 kg; 95% CI, -2.55 to -1.83) compared to albiglutide (-0.64 kg; -1.00 to -0.28); corresponding to a treatment difference at week 32 of 1.55 kg (95% CI, 1.05 to 2.06; P<0.0001). At week 32, the LSM change (SD) in weight from baseline was -2.2 kg (4.15) in patients treated with liraglutide compared to -0.6 kg (3.12) with albiglutide.</p> <p>The most common adverse events were injection-site reactions, GI events, and upper respiratory tract infections. GI events were common in both groups occurring at a frequency of 35.9% in albiglutide-treated patients and 49.0% in liraglutide-treated patients; corresponding to a treatment difference of -13.1%</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(95% CI, -19.9 to -6.4). Diarrhea was the most common GI event in the albiglutide group and occurred more frequently than the liraglutide group, although the difference was not significant. Investigator-assessed cardiovascular adverse events occurred at a similar rate in the albiglutide group (8.2%) and the liraglutide group (10.5%); corresponding to a treatment difference of -2.4% (95% CI, -6.4 to 1.6).
Reusch et al. ³⁵ (2014) HARMONY 1 Albiglutide (30 mg once a week) vs placebo	DB, PC, RCT Patients ≥18 years of age with a BMI of 20 to 45 kg/m ² , diagnosed with type 2 diabetes, HbA _{1c} 7.0 to 10.0% on stable doses of pioglitazone (≥30 mg pioglitazone daily or the patient's maximum tolerated dose) with or without a stable dose of metformin (≥1500 mg or maximum tolerated dose) for at least 2 months before randomization	N=310 3 years	Primary: Change in HbA _{1c} from baseline to 52 weeks Secondary: Changes in HbA _{1c} over time, FPG (change from baseline at week 52 and over time), time to hyperglycaemia rescue, percent of patients attaining HbA _{1c} of <6.5 and <7.0%, and change from baseline in body weight	Primary: The model-adjusted change from baseline in HbA _{1c} at week 52 was significantly improved with albiglutide than with placebo (-0.8%; 95% CI, -1.0 to -0.6; P<0.0001). Secondary: Change from baseline FPG was -1.3 mmol/l in the albiglutide group and 0.4 mmol/l in the placebo group (P<0.0001); a significantly higher percentage of patients reached the HbA _{1c} goals with albiglutide (P<0.0001), and the rate of hyperglycaemia rescue up to week 52 for albiglutide was 24.4 versus 47.7% for placebo (P<0.0001). Albiglutide plus pioglitazone had no impact on weight, and severe hypoglycaemia was observed rarely (n = 2). With few exceptions, the results of safety assessments were similar between the groups, and most adverse events were mild or moderate. The 52-week incidence rates for gastrointestinal adverse events for albiglutide and placebo were: 31.3 and 29.8%, respectively (diarrhea: 11.3 and 8.6%; nausea: 10.7 and 11.3%; vomiting: 4.0 and 4.0%).
Weissman et al. ³⁶ (2014) HARMONY 4 Albiglutide (30 mg once a week) vs insulin glargine	MC, OL, NI, RCT Patients ≥18 years of age with type 2 diabetes treated with metformin (±sulfonylurea) for at least 3 months with a baseline HbA _{1c} 7.0 to 10.0%	N=779 52 weeks	Primary: Change in HbA _{1c} from baseline to 52 weeks Secondary: Change from baseline in FPG at week 52, changes from baseline in	Primary: In the albiglutide group, HbA _{1c} declined from 8.28 ± 0.90% (mean ± SD) at baseline to 7.62 ± 1.12% at week 52. A similar reduction occurred in the insulin glargine group (8.36 ± 0.95% to 7.55 ± 1.04%). The model-adjusted treatment difference of 0.11% (95% CI, -0.04% to 0.27%) indicated non-inferiority of albiglutide to insulin glargine based on the pre-specified non-inferiority margin of 0.3% (P=0.0086). Secondary: At week 52, FPG had declined by a mean 0.87 mmol/l in the albiglutide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(10 U once a day)			HbA _{1c} and FPG over time, time to hyperglycaemic rescue, proportion of patients achieving HbA _{1c} goals, body weight	group and by 2.06 mmol/l in the insulin glargine group; the treatment difference was significant in favour of insulin glargine (P<0.0001). Body weight increased in the insulin glargine group and decreased in the albiglutide group, with a mean treatment difference of -2.61 kg (95% CI, -3.20 to -2.02; P<0.0001). Documented symptomatic hypoglycaemia occurred in a higher proportion of patients in the insulin glargine group than in the albiglutide group (27.4 vs 17.5%, P=0.0377).
Home et al. ³⁷ (2015) HARMONY 5 Albiglutide (30 mg/week) vs pioglitazone (30 mg/day) vs placebo current dose of metformin (>1500 mg/day) was maintained throughout and blinded uptitration of study drug was allowed	DB, MC, PG, RCT Patients ≥18 years of age with a historical diagnosis of type 2 diabetes and inadequate glycaemic control on their current regimen of metformin and a sulfonylurea	N=685 156 weeks	Primary: Change in HbA _{1c} from baseline to 52 weeks Secondary: HbA _{1c} change over time, FPG, HbA _{1c} responders, body weight change, adverse events	Primary: The week 52 model-adjusted difference in change in HbA _{1c} for albiglutide versus placebo was -0.87 (95% CI, -1.07 to -0.68)%-units (P<0.001), and for albiglutide versus pioglitazone it was 0.25 (95% CI, 0.10 to 0.40)%-units; therefore, not non-inferior. Secondary: In the albiglutide group only, fasting plasma glucose reduced rapidly in the first two weeks. Confirmed hypoglycemia occurred in 14% of participants on albiglutide, 25% on pioglitazone and 14% on placebo. The mean (± standard error) weight change was -0.42 (±0.2) kg with albiglutide, 4.4 (±0.2) kg (P<0.001) with pioglitazone, and -0.40 (±0.4) kg with placebo and serious adverse events occurred in 6.3, 9.0 and 6.1% of participants in the respective groups. Injection site reactions occurred in 13% of participants on albiglutide and resulted in treatment discontinuation for four participants (1.4%).
Leiter et al. ³⁸ (2014) Albiglutide 30 mg once weekly (uptitrated if needed)	DB, MC, RCT Renally impaired patients with type 2 diabetes	N=507 52 weeks	Primary: Change in HbA _{1c} from baseline to 26 weeks Secondary: FPG, weight,	Primary: The model-adjusted LS mean for the primary end point of change from baseline in HbA _{1c} at week 26 was -0.83% in the albiglutide group and -0.52% in the sitagliptin group, with similar results across all three baseline eGFR groups. The treatment difference (albiglutide vs sitagliptin) was -0.32% (95% CI, -0.49 to -0.15). The upper bound of the CI was below the prespecified noninferiority margin of 0.4%, indicating noninferiority of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>sitagliptin (dosed based on the eGFR value)</p> <p>Patients continued to receive their prescribed oral antihyperglycemic medication regimen (metformin, thiazolidinedione, sulfonylurea, or any combination of these oral antihyperglycemic medications).</p>			<p>achievement of treatment targets, hyperglycemic rescue, and safety.</p>	<p>albiglutide to sitagliptin. A superiority test conducted in accordance with a prespecified, step-wise procedure indicated that albiglutide was statistically superior to sitagliptin (P=0.0003). The treatment effect of albiglutide seen at week 26 was maintained through week 52.</p> <p>Secondary: The change in FPG from baseline at week 26 was -1.42 mmol/L in the albiglutide group and -0.22 mmol/L in the sitagliptin group. At week 26, the difference in LS means (albiglutide vs sitagliptin) was -1.20 mmol/L (P<0.0001). A higher percentage of patients in the albiglutide treatment group achieved the treatment targets of HbA_{1c} <6.5% and <7.0% at week 26 (albiglutide 15.3% and 42.6%, respectively, compared with sitagliptin 12.3% and 30.5%, respectively). The treatment difference between albiglutide and sitagliptin was statistically significant (P=0.0077) for the treatment target of HbA_{1c} <7.0% at week 26. There was a statistically significant difference between albiglutide and sitagliptin (P=0.0017) in the mean time to hyperglycemia rescue through week 52. The proportion of patients who had required hyperglycemia rescue was lower in the albiglutide group than in the sitagliptin group at week 26 (6.1% [15 patients] vs 12.1% [29 patients]) and at week 52 (17.9% [44 patients] vs 28.3% [68 patients]). Patients in both treatment groups showed a modest mean loss in body weight through week 26, with a model-adjusted LS mean weight change from baseline of -0.79 kg for albiglutide and -0.19 kg for sitagliptin (P<0.05). The incidence of any adverse event and the event rates of on-therapy adverse events over the course of the study were similar between the two treatment groups (83.5% and 347 AEs/100 person-years with albiglutide and 83.3% and 331 AEs/100 person-years with sitagliptin).</p>
<p>Giorgino et al.³⁹ (2015) AWARD-2</p> <p>Dulaglutide 1.5 mg once-weekly</p> <p>vs</p> <p>dulaglutide 0.75 mg once-weekly</p>	<p>OL, MC, RCT</p> <p>Adults with an HbA_{1c} of ≥7.0% and ≤11.0%, BMI ≥23 and ≤45 kg/m², and stable weight for ≥3 months, who were not optimally controlled with one, two, or three oral</p>	<p>N=810</p> <p>78 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to 52 weeks</p> <p>Secondary: Changes in HbA_{1c} from baseline to 26 and 78 weeks, the percentage of patients achieving</p>	<p>Primary: The mean HbA_{1c} change from baseline to the 52-week primary end point was -1.08 ± 0.06%, -0.76 ± 0.06%, and -0.63 ± 0.06% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively. Statistical criteria for superiority was met with dulaglutide 1.5 mg, LS mean difference of -0.45% (95% CI, -0.60 to -0.29; adjusted one-sided P<0.001). Statistical criteria for noninferiority were met for dulaglutide 0.75 mg, -0.13% (95% CI, -0.29 to 0.02; adjusted one-sided P<0.001).</p> <p>Secondary: There was no significant difference in percentages of patients who achieved</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs once-daily glargine</p>	<p>antihyperglycemic medications (of which one had to be metformin or a sulfonylurea) for at least three months</p>		<p>HbA_{1c} <7.0% and ≤6.5%, and changes in FPG, 8-point self-monitored plasma glucose profiles, adverse events</p>	<p>the HbA_{1c} target of <7.0% for dulaglutide 0.75 mg (37.1%) compared with glargine. Greater percentages of patients on dulaglutide 1.5 mg (27.0%) and dulaglutide 0.75 mg (22.5%) achieved an HbA_{1c} target ≤6.5% than with glargine (13.5%) (P<0.001 and P=0.004, respectively). At 78 weeks, percentages of patients attaining HbA_{1c} targets were generally maintained, except for the percentage of patients with an HbA_{1c} of ≤6.5%, which was similar for dulaglutide 0.75 mg and glargine. At 52 weeks, the FPG from 8-point SMPG profiles decreased more with glargine than with dulaglutide 1.5 mg and dulaglutide 0.75 mg. More patients on dulaglutide 1.5 mg achieved HbA_{1c} targets <7.0% versus glargine (P<0.001). Body weight decreased with dulaglutide and increased with glargine. Total hypoglycemia rates were lower with dulaglutide; severe hypoglycemia was minimal. Increases in pancreatic enzymes were observed for dulaglutide. Incidence of nausea (15.4, 7.7, and 1.5%) and diarrhea (10.6, 9.2, and 5.7%) were more common with dulaglutide 1.5 mg and 0.75 mg than with glargine.</p>
<p>Blonde et al.⁴⁰ (2015) AWARD-4 Dulaglutide 1.5 mg once-weekly vs dulaglutide 0.75 mg once-weekly vs daily bedtime glargine All groups also used a lispro dosing algorithm, and metformin was allowed</p>	<p>NI, OL, RCT Patients (≥18 years of age) with type 2 diabetes inadequately controlled with conventional insulin treatment</p>	<p>N=884 52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to 26 weeks Secondary: The proportion of patients achieving HbA_{1c} of < 7.0% or of ≤6.5%, change in FPG, self-monitored plasma glucose, bodyweight, BMI, insulin doses, and patient-reported outcomes</p>	<p>Primary: At 26 weeks, the adjusted mean change in HbA_{1c} was greater in patients receiving dulaglutide 1.5 mg (-1.64%; 95% CI, -1.78 to -1.50) and dulaglutide 0.75 mg (-1.59%; 95% CI, -1.73 to -1.45) than in those receiving glargine (-1.41%; 95% CI, -1.55 to -1.27). The adjusted mean difference versus glargine was -0.22% (95% CI, -0.38 to -0.07; P=0.005) for dulaglutide 1.5 mg and -0.17% (95% CI, -0.33 to -0.02; P=0.015) for dulaglutide 0.75 mg. Secondary: At 26 weeks, the proportion of patients achieving an HbA_{1c} target of <7.0% was significantly greater in both the dulaglutide 1.5 mg and 0.75 mg groups versus glargine (P=0.014 and P=0.010, respectively). Compared with glargine, a significantly greater proportion of patients in the dulaglutide 1.5 mg group (P=0.027) also achieved an HbA_{1c} target of 6.5% or less at 26 weeks. At 52 weeks, a significantly greater proportion of patients in the dulaglutide 1.5 mg group achieved HbA_{1c} <7.0% versus glargine (P=0.0499). The proportion of patients achieving HbA_{1c} of 6.5% or less at week 52 did not differ significantly between the dulaglutide 1.5 mg and 0.75 mg groups and the glargine group (P=0.27 and P=0.62). For the composite endpoints assessing the proportion of patients achieving HbA_{1c} <7.0% without documented symptomatic hypoglycaemia and,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>separately, without nocturnal or severe hypoglycaemia, alone or in combination with no weight gain, significantly more patients met the criteria in the dulaglutide 1.5 mg group than the glargine group at both weeks 26 and 52 (all P<0.05).</p> <p>The reductions in adjusted mean FPG from baseline to week 26 were significantly greater with glargine (-1.58 mmol/L; 95% CI, -1.97 to -1.19) than with dulaglutide 1.5 mg (-0.27 mmol/L; 95% CI, -0.66 to 0.12; P<0.0001) or dulaglutide 0.75 mg (0.22 mmol/L; 95% CI, -0.17 to 0.61; P<0.0001); results were similar at week 52 (both P<0.0001). The self-monitored plasma glucose values (8-point daily profile) at 26 weeks decreased at each timepoint compared with baseline in all groups.</p> <p>The adjusted mean changes in bodyweight at 26 weeks were -0.87 kg (95% CI, -1.40 to -0.34) in the dulaglutide 1.5 mg group, 0.18 kg (95% CI, -0.35 to 0.71) in the dulaglutide 0.75 mg group, and 2.33 kg (1.80 to 2.86) in the glargine group. The differences between the dulaglutide and glargine groups were significant (all P<0.0001) and similar differences were noted at 52 weeks. Between-group differences for change in BMI were consistent with weight findings.</p>
<p>Dungan et al.⁴¹ (2014) AWARD-6</p> <p>Dulaglutide 1.5 mg once-weekly</p> <p>vs</p> <p>liraglutide 1.8 mg once-daily</p>	<p>MC, NI, OL, RCT</p> <p>Metformin-treated patients with uncontrolled type 2 diabetes</p>	<p>N=599</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: proportion of patients achieving HbA_{1c} targets, change in FPG, self-monitored plasma glucose, BMI, safety</p>	<p>Primary: Both dulaglutide and liraglutide significantly reduced HbA_{1c} from baseline. The HbA_{1c} reduction with dulaglutide was non-inferior, but not superior, to that achieved by liraglutide, with a between-group difference in HbA_{1c} reduction from baseline of -0.06% (95% CI, -0.19 to 0.07; P_{non-inferiority}<0.0001). Decreases in HbA_{1c} over time were similar between groups.</p> <p>Secondary: At 26 weeks, 200 of 293 (68%) patients in the dulaglutide group achieved HbA_{1c} targets of less than 7.0% compared with 199 of 293 (68%) in the liraglutide group; 160 (55%) patients achieved HbA_{1c} targets of 6.5% or less in the dulaglutide group compared with 149 (51%) in the liraglutide group. Both dulaglutide and liraglutide significantly reduced FPG concentrations between baseline and 26 weeks, with no significant difference between groups. Seven-point self-monitored plasma glucose profiles measured at baseline and 26 weeks did not differ significantly between treatments at any time point measured. The mean change from baseline in bodyweight was -2.90 kg for dulaglutide and -3.61 kg for liraglutide; between-group</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				differences for change from baseline in BMI were consistent with weight findings. The most frequent treatment emergent adverse events were generally gastrointestinal, with nausea, diarrhoea, vomiting, and dyspepsia being the most common; there were no differences between groups.
Dungan et al. ⁴² (2016) AWARD-8 Dulaglutide 1.5 mg once-weekly vs placebo	DB, PC, RCT Sulphonylurea-treated (≥half-maximal dose, stable ≥3 months) patients with type 2 diabetes and inadequate glycaemic control (HbA _{1c} ≥7.5 and ≤9.5%)	N=300 24 weeks	Primary: HbA _{1c} change from baseline at 24 weeks Secondary: proportion of patients achieving HbA _{1c} targets, change in FPG, self-monitored plasma glucose, body weight, safety	Primary: Dulaglutide reduced HbA _{1c} by -1.4% from baseline compared with -0.1% for placebo, with a between-group difference of -1.3% (95% CI, -1.6 to -1.0; P<0.001). This significant difference met the primary endpoint of superiority versus placebo for this study. Dulaglutide significantly improved HbA _{1c} versus placebo at all post-baseline time points, beginning at four weeks. Secondary: At 24 weeks, 55.3% (dulaglutide) and 18.9% (placebo) of participants achieved an HbA _{1c} target of <7.0% (P<0.001 dulaglutide vs placebo), while 40% (dulaglutide) and 9.4% (placebo) of participants achieved an HbA _{1c} target of ≤6.5% (P<0.001 dulaglutide vs placebo). Dulaglutide reduced FPG from baseline to 24 weeks (dulaglutide -1.70 and placebo 0.16 mmol/l); the between-group least-squares (LS) mean difference of -1.86 mmol/l (95% CI, -2.58 to -1.14) was statistically significant (-33.54 mg/dl; 95% CI, -46.55 to -20.53; P<0.001). At all time points, the LS mean values for seven-point self-monitored plasma glucose were significantly reduced in the dulaglutide-treated group (all P<0.001). The LSM change in weight from baseline was -0.91 kg for dulaglutide (P<0.001) and -0.24 kg for placebo (P=0.553). The between-group difference was not significant with an LS mean of -0.68 kg (95% CI, -1.53 to 0.18; P=0.120). A similar proportion of participants experienced treatment-emergent adverse events in the dulaglutide group (n = 111, 46.4%) compared with the placebo group (n = 23, 38.3%; P=0.259).
Weinstock et al. ⁴³ (2015) AWARD-5 Dulaglutide (1.5 or 0.75 mg) vs sitagliptin 100 mg	DB, MC, RCT Patients 18 to 75 years of age with type 2 diabetes (≥6 months' duration) and an HbA _{1c} value of >8.0% and ≤9.5% on diet and exercise	N=1,098 104 weeks	Primary: HbA _{1c} Secondary: Percentage of participants achieving an HbA _{1c} target of <7.0% and ≤6.5%; body weight; FPG	Primary: Changes in HbA _{1c} at 104 weeks were (least squares mean ± standard error) -0.99 ± 0.06%, -0.71 ± 0.07% and -0.32 ± 0.06% for dulaglutide 1.5 mg, dulaglutide 0.75 mg and sitagliptin, respectively (P<0.001, both dulaglutide doses vs sitagliptin). Secondary: At 104 weeks, the percentage of participants attaining the HbA _{1c} target goal of <7.0% was significantly higher in the dulaglutide 1.5 mg and dulaglutide 0.75 mg arms (54 and 45%, respectively) compared with sitagliptin (31%);

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>alone, or $\geq 7.0\%$ and $\leq 9.5\%$ on monotherapy or combination therapy (metformin plus another oral antihyperglycaemic medication), and a BMI of 25 to 40 kg/m^2</p>		<p>and fasting insulin; β-cell function; lipids; safety</p>	<p>$P < 0.001$, both comparisons). Additionally, 39 and 24% of participants in the dulaglutide 1.5 mg and dulaglutide 0.75 mg arms, respectively, achieved HbA_{1c} targets of $\leq 6.5\%$, compared with 14% in the sitagliptin arm ($P < 0.001$, both comparisons).</p> <p>The measurement of insulin sensitivity (HOMA2-%S) was not different between treatment groups, while β-cell function, as assessed by HOMA2-%β, increased significantly more with dulaglutide 1.5 mg and dulaglutide 0.75 mg than with sitagliptin. Weight loss was greater with dulaglutide 1.5 mg ($P < 0.001$) and similar with 0.75 mg versus sitagliptin (2.88 ± 0.25, 2.39 ± 0.26 and 1.75 ± 0.25 kg, respectively). Gastrointestinal adverse events were more common with dulaglutide 1.5 and 0.75 mg versus sitagliptin (nausea 17 and 15% vs 7%, diarrhoea 16 and 12% vs 6%, vomiting 14 and 8% vs 4% respectively). Pancreatic, thyroid, cardiovascular and hypersensitivity safety were similar across groups.</p>
<p>Buse et al.⁴⁴ (2011)</p> <p>Exenatide 5 μg SC BID for 4 weeks, followed by 10 μg SC BID</p> <p>vs</p> <p>placebo</p> <p>All patients also received optimized insulin glargine dosing (at randomization, patients with HbA_{1c} levels $> 8.0\%$ continued to receive current insulin glargine dose; those with</p>	<p>DB, MC, PC, RCT</p> <p>Type 2 diabetics ≥ 18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥ 3 months, HbA_{1c} 7.1 to 10.5%, BMI $\leq 45 \text{ kg/m}^2$, and stable body weight over past 3 months</p>	<p>N=261</p> <p>30 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving HbA_{1c} ≤ 7.0 or $\leq 6.5\%$; seven-point self-monitored glucose concentrations; change in baseline body weight, waist circumference, and insulin dose; safety</p>	<p>Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-1.74 vs -1.04%; $P < 0.001$).</p> <p>Secondary: A significantly greater proportion of patients receiving exenatide achieved an HbA_{1c} $\leq 7.0\%$ (60 vs 35%; treatment difference, 25%; 95% CI, 12 to 39; $P < 0.001$). Similar results were observed with HbA_{1c} $\leq 6.5\%$ (40 vs 12%; treatment difference, 28%; 95% CI, 17 to 39; $P < 0.001$).</p> <p>With regards to seven-point self-monitored glucose concentrations, exenatide significantly decreased concentrations during morning and evening time points compared to placebo ($P < 0.001$), but not at midday ($P = 0.320$).</p> <p>Exenatide significantly decreased body weight compared to placebo (-1.8 vs 1.0 kg; $P < 0.001$), but no difference between treatments was observed in waist circumference ($P = 0.23$).</p> <p>The number of hypoglycemic events per-participant per-year did not differ between the exenatide and placebo ($P = 0.49$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>HbA_{1c} ≤8.0% decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to titrate to achieve a fasting glucose level ≤100 mg/dL).</p>				
<p>Rosenstock et al.⁴⁵ (2012)</p> <p>Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID</p> <p>vs</p> <p>placebo</p> <p>All patients also received optimized insulin glargine dosing (at randomization, patients with HbA_{1c} levels >8.0% continued to receive current insulin glargine dose; those with HbA_{1c} ≤8.0% decreased their dose by 20%; these doses were maintained for 5</p>	<p>Exploratory analysis of Buse et al.³¹</p> <p>Baseline factors associated with glycemic control and weight loss in type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥3 months, HbA_{1c} 7.1 to 10.5%, BMI ≤45 kg/m², and stable body weight over past 3 months</p>	<p>N=259</p> <p>30 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, weight</p> <p>Secondary: Not reported</p>	<p>Primary: Patients receiving exenatide had achieved significantly greater reductions in HbA_{1c} compared to patients receiving placebo, irrespective of baseline HbA_{1c} (P<0.001).</p> <p>Patients receiving exenatide with longer duration of diabetes and those with lower BMI achieved significantly greater reductions in HbA_{1c} compared to patients receiving placebo (P<0.01).</p> <p>Patients receiving exenatide lost significantly more weight, regardless of baseline HbA_{1c} or BMI compared to patients receiving placebo (P<0.05).</p> <p>Patients receiving exenatide with longer duration of diabetes lost the most weight compared to patients receiving placebo (P<0.001).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>weeks, after which patients began to titrate to achieve a fasting glucose level ≤ 100 mg/dL).</p>				
<p>Okerson et al.⁴⁶ (2010)</p> <p>Exenatide 5 μg SC BID for 4 weeks, followed by 10 μg SC BID</p> <p>vs</p> <p>placebo or insulin</p> <p>All patients also received existing antidiabetic treatment regimens.</p>	<p>Post-hoc analysis (6 RCTs)</p> <p>Type 2 diabetics ≥ 18 years of age with HbA_{1c} ≥ 6.5 to $\leq 11.0\%$, BMI ≥ 25 to ≤ 45 kg/m², and stable body weight</p>	<p>N=2,171</p> <p>24 to 52 weeks</p>	<p>Primary: Change in baseline BP and pulse pressure</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.20 ± 0.56 vs 0.60 ± 0.56 mm Hg; treatment difference, -2.80 ± 0.75 mm Hg; P=0.002) and insulin (-4.5 ± 0.6 vs -0.9 ± 0.6 mm Hg; treatment difference, -3.7 ± 0.85 mm Hg; P<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.70 ± 0.33 vs -0.20 ± 0.33 mm Hg; P=0.21) or insulin (-1.60 ± 0.35 vs -0.80 ± 0.36 mm Hg; P=0.16). No differences in the proportions of patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference, -3.8 mm Hg; P=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; P<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (P values not reported).</p> <p>Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥ 40 mm Hg. In this subgroup, the reduction in pulse pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; P<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; P<0.0001).</p> <p>By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment difference, 19%; P=0.03); however, no treatment effect on DBP was observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of exenatide-treated patients were favorably shifted from a baseline classification of “abnormal DBP” to “normal DBP” compared to placebo</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(treatment difference, 41.4 vs 32.4%; P=0.02). Secondary: Not reported
Buse et al. ⁴⁷ DURATION-6 (2013) Exenatide 2 mg weekly vs liraglutide 1.8 mg QD	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes treated with lifestyle modification and oral antihyperglycemic drugs (metformin, sulfonylurea, metformin plus sulfonylurea, or metformin plus pioglitazone) with suboptimal glycemic control	N=911 26 weeks	Primary: Change in HbA _{1c} at week 26 from baseline between exenatide and liraglutide Secondary: Proportion of patients achieving HbA _{1c} <7%; changes in bodyweight; concentrations of fasting serum glucose; BP; serum lipid concentrations; rates of hypoglycemia; safety and tolerability; patient-reported outcomes	Primary: Both drugs were associated with a clinically important decrease in HbA _{1c} from baseline. Change in HbA _{1c} at endpoint was greater in patients taking liraglutide than in those taking exenatide (P=0.02). Secondary: 60% of patients receiving liraglutide and 53% receiving exenatide achieved HbA _{1c} of less than 7% (P=0.0011). Both treatments were associated with progressive decreases in bodyweight. Patients taking liraglutide lost more weight than did those taking exenatide, irrespective of BMI. At 26 weeks, fasting serum glucose significantly decreased in both groups (P<0.0001), but the decrease was greater in patients in the liraglutide group than in those in the exenatide group (P=0.02). Patients in both groups had similar decreases in BP. Improvements in other cardiovascular biomarkers (lipids, C-reactive protein, and brain natriuretic peptide) were similar between groups at endpoint. The most common adverse events were mainly gastrointestinal in both groups, with a greater frequency of nausea, diarrhea, and vomiting in patients in the liraglutide group than in those in the exenatide group.
Gallwitz et al. ⁴⁸ EUREXA (2012) Exenatide 5 to 10 µg BID vs glimepiride 1 mg	MC, OL, RCT Overweight patients aged 18 to 85 years with type 2 diabetes on a stable maximum tolerated dose of metformin with HbA _{1c} between 6.5 and 9.0%	N=977 Average treatment was 2 years	Primary: Time to inadequate glycemic control (HbA _{1c} >9% after the first 3 months, or >7% at 2 consecutive visits 3 months apart after the first 6 months)	Primary: Median time to inadequate HbA _{1c} control was 180 weeks with exenatide versus 142.1 weeks with glimepiride (P=0.032). In the exenatide group, 203 (41%) patients had treatment failure compared with 262 (54%) in the glimepiride group (risk difference, 12.4; 95% CI, 6.2 to 18.6; HR, 0.748; CI, 0.623 to 0.899; P=0.002). Secondary: Systolic blood pressure decreased in patients in the exenatide group (change

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
initially, titrated to maximum tolerated dose			Secondary: Markers of β -cell function, bodyweight, hypoglycemia, surrogate markers of cardiovascular risk (blood pressure and heart rate)	to endpoint -1.9 mmHg; P=0.006), but not in the glimepiride group (1.1 mmHg; P=0.096). Heart rate increased at endpoint in patients given exenatide (1.2 beats per min (bpm); P=0.024), but not in those given glimepiride (0.6 bpm; P=0.282), with no difference between groups at any time. Discontinuation because of adverse events (mainly gastrointestinal) was significantly higher (P=0.0005) in the exenatide group than in the glimepiride group in the first six months of treatment, but not thereafter.
Buse et al. ⁴⁹ (2004) Exenatide 5 μ g BID and sulfonylurea (existing therapy) vs exenatide 10 μ g BID and sulfonylurea (existing therapy) vs sulfonylurea (existing therapy) and placebo	MC, PC, PG, RCT, TB Type 2 diabetic patients 22 to 76 years of age, treated with maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥ 3 months, FPG <240 mg/dL, BMI 27 to 45 kg/m ² , HbA _{1c} 7.1 to 11.0%, stable weight ($\pm 10\%$) for 3 months prior to	N=377 30 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipoproteins	Primary: Significantly greater decreases in HbA _{1c} were noted with exenatide 10 (-0.86%) and 5 μ g (-0.46%) compared to placebo (0.12%; P<0.0002 for pairwise comparison). Secondary: A significantly greater decreases in FPG was reported with exenatide 10 μ g at week 30 compared to placebo (-0.6 vs 0.4 mmol/L; P<0.05). There was no difference between exenatide 5 μ g and placebo (P value not reported). A significantly greater decrease in body weight was noted with exenatide 10 μ g at week 30 compared placebo (-1.6 vs -0.6 kg; P<0.05). There was no difference between exenatide 5 μ g and placebo (P value not reported). There were no differences in fasting insulin concentrations between any of the treatments (P value not reported). A significantly greater decrease in fasting proinsulin concentrations was noted with exenatide 10 μ g at week 30 compared to placebo (-16 mmol/L; P<0.01). A similar trend was reported with exenatide 5 μ g compared to placebo, but no significance was reported (P value not reported). There was a small decrease in LDL-C and apo B (P<0.05 for pairwise comparisons for both values) with exenatide compared to placebo. No differences were observed in other lipid parameters evaluated (P values not reported). Side effects reported by patients receiving exenatide 10 μ g included nausea

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	screening, and no lab value >25% outside of normal value			<p>(51%), vomiting (13%), diarrhea (9%), constipation (9%), and hypoglycemia (36%) (P values not reported).</p> <p>There were 13 (10.1%) withdrawals due to adverse event(s) with exenatide 10 µg compared to nine (7.2%) withdrawals with exenatide 5 µg and four (3.3%) withdrawals with placebo (P values not reported). The majority of the events reported were mild to moderate in nature. Serious adverse events were reported in 4, 3, and 8% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo. Such events included a MI in an exenatide-treated patient and one placebo-treated patient who experienced clinical manifestations of coronary artery disease.</p>
<p>DeFronzo et al.⁵⁰ (2005)</p> <p>Exenatide 5 µg BID and metformin (existing therapy)</p> <p>vs</p> <p>exenatide 10 µg BID and metformin (existing therapy)</p> <p>vs</p> <p>metformin (existing therapy) and placebo</p>	<p>MC, PC, PG, RCT, TB</p> <p>Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m², HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value</p>	<p>N=336</p> <p>30 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving HbA_{1c} ≤7.0%; change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipids</p>	<p>Primary: Significantly greater decreases in HbA_{1c} were reported with exenatide 10 (-0.78%) and 5 µg (-0.40%) compared to placebo (0.08%; P<0.002 for pairwise comparison).</p> <p>Secondary: A significantly greater proportion of patients achieved HbA_{1c} ≤7.0% with exenatide 5 (27%) and 10 µg (40%) compared to placebo (11%; P<0.01 for pairwise comparison).</p> <p>Significantly greater decreases in FPG were observed with exenatide 5 (-7.2 mg/dL; P<0.005) and 10 µg (-10.1 mg/dL; P<0.0001) compared to placebo (14.4 mg/dL).</p> <p>Significantly greater decreases in body weight were observed with exenatide 5 (-1.6 kg; P<0.05) and 10 µg (-2.8 kg; P<0.001) compared to placebo (-0.3 kg).</p> <p>There was no difference in fasting insulin or proinsulin concentrations between any of the treatments (P values not reported).</p> <p>No differences in lipid profiles were observed between any of the treatments (P value not reported).</p> <p>Gastrointestinal side effects were most commonly reported with exenatide and included nausea (45%), diarrhea (16%), and vomiting (12%) in exenatide 10 µg-treated patients (P values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Kendall et al.⁵¹ (2005)</p> <p>Exenatide 5 µg BID and oral hypoglycemic therapy (existing therapy)</p> <p>vs</p> <p>exenatide 10 µg BID and oral hypoglycemic therapy (existing therapy)</p> <p>vs</p> <p>oral hypoglycemic therapy (existing therapy) and placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetic patients 22 to 77 years of age, treated with maximally effective doses of metformin (≥1,500 mg/day) and a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) for ≥3 months before screening, FPG <13.3 mmol/L, BMI 27 to 45 kg/m², HbA_{1c} 7.5 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25%</p>	<p>N=733</p> <p>30 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, PPG, and body weight</p>	<p>The incidence of hypoglycemia was similar with all treatments. Withdrawals due to adverse event(s) occurred in 7.1, 3.6, and 0.9% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported).</p> <p>Primary: Significantly greater decreases in HbA_{1c} were achieved with exenatide 5 (-0.55±0.07%) and 10 µg (-0.77±0.08%) compared to placebo (0.23±0.07%; P<0.001 for pairwise comparison).</p> <p>Secondary: Significantly greater decreases in FPG were achieved with exenatide 5 (-0.5±0.2 mmol/L) and 10 µg (-0.6±0.2 mmol/L) compared to placebo (0.8±0.2 mmol/L; P<0.0001 for pairwise comparison).</p> <p>Significantly greater decreases in PPG were achieved with exenatide 5 (P=0.009) and 10 µg (P=0.0004) compared to placebo.</p> <p>Significantly greater decreases in body weight were achieved with exenatide 5 (-1.6±0.2 kg) and 10 µg (-1.6±0.2 kg) compared to placebo (-0.9±0.2 kg; P≤0.01).</p> <p>Nausea was the most commonly reported adverse event and was observed in 48.5, 39.2, and 20.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported). A higher incidence of hypoglycemia was reported with exenatide. Hypoglycemia was reported in 27.8, 19.2, and 12.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	outside of normal value			
Abdul-Ghani et al. ⁵² (2015) EDICT Metformin (escalating dose) vs Triple therapy (metformin/pioglitazone/exenatide)	OL, RCT Drug-naïve, recently diagnosed (<2 years) subjects 30 to 75 years of age with type 2 diabetes mellitus	N=221 2 years	Primary: HbA _{1c} Secondary: Percentage of participants achieving HbA _{1c} <6.5 and <7.0%; decrease in fasting and postprandial plasma glucose; change in body weight; and rate of hypoglycaemic events	Primary: Baseline HbA _{1c} was identical in both groups (8.6%) and during the first six months decreased in both treatment arms. At six months, there was a small but significant HbA _{1c} difference (0.2%, P=0.03) between groups (triple therapy 6.0% vs metformin therapy 6.2%). After six months, HbA _{1c} gradually increased with metformin therapy to 6.5% at 24 months and remained stable at 5.95% with triple therapy; thus, the difference in HbA _{1c} between the two treatments progressively increased with time and was significantly different at two years (change in HbA _{1c} 0.55%; P<0.0001). Secondary: More participants receiving metformin therapy failed to maintain the treatment goal (HbA _{1c} <6.5%) than did those receiving triple therapy (44 vs 17%; P=0.003). A total of 40 participants receiving metformin therapy failed to maintain HbA _{1c} at <6.5% at/after six months compared with only 13 participants receiving triple therapy (P<0.0001). More participants receiving triple therapy (61%) had HbA _{1c} reduced to the normal range (<6.0%) than those receiving metformin therapy (27%; P<0.0001). The median HbA _{1c} of participants receiving triple therapy was 5.9% compared with 6.4% for those receiving metformin therapy. More than 90% of participants receiving triple therapy maintained HbA _{1c} at <7.0% versus <75% of participants receiving metformin therapy. The most common adverse event was hypoglycaemia, reported by 46 and 14% of participants receiving metformin and triple therapy, respectively. The overall frequency of hypoglycaemic events was greater in participants receiving metformin therapy (2.2 vs 0.31 events/participant per year; P<0.0001).
Schernthaler et al. ⁵³ (2015) EUREXA TZD or glimepiride added to metformin plus	MC, OL, RCT Patients with type 2 diabetes with metformin failure (HbA _{1c} ≥6.5 to ≤9.0%), were 19 to 85 years of age and	N=310 Median duration of 2 years	Primary: Changes in HbA _{1c} , BMI, lipids, hypoglycaemia, and vital signs Secondary: Not reported	Primary: Significant changes from baseline in HbA _{1c} were observed at 52, 78, 104 and 130 weeks with add-on TZD (all P<0.01), but only at 52 weeks with add-on glimepiride (P=0.001). Significant between-group differences favouring add-on TZD were observed at 78 (P=0.004) and 130 weeks (P=0.001). Among patients re-randomized to add-on glimepiride and add-on TZD, HbA _{1c} ≤7.0% was achieved by 26.0 and 30.7%, respectively, and HbA _{1c}

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>exenatide twice daily</p> <p>vs</p> <p>exenatide twice daily added to metformin plus glimepiride</p>	<p>had a BMI of ≥ 25 to ≤ 40 kg/m²</p>			<p>$\leq 6.5\%$ by 8.2 and 9.3%, respectively (no significant differences between the randomized groups).</p> <p>BMI significantly increased from baseline at 52, 78, 104 and 130 weeks with add-on TZD (all $P \leq 0.01$), but significantly increased at 52 and 78 weeks (both $P < 0.05$) and decreased at 130 weeks with add-on glimepiride; the between-group difference was significant at 104 ($P = 0.022$) and 130 weeks ($P = 0.008$).</p> <p>HDL cholesterol significantly increased from baseline to 130 weeks in the TZD add-on group ($P < 0.001$), but not in the add-on glimepiride group; the between-group difference significantly favoured TZD ($P < 0.001$). For total and LDL cholesterol, there were no significant within- or between-group changes from baseline to 130 weeks.</p> <p>Systolic blood pressure was significantly increased at 130 weeks with add-on TZD ($P = 0.043$), but not with add-on glimepiride; the between-group difference significantly favoured glimepiride ($P = 0.044$).</p> <p>The incidence of any hypoglycaemia and nocturnal, non-nocturnal and documented symptomatic hypoglycaemia with blood glucose ≤ 70 mg/dl was significantly higher for glimepiride than TZD as add-on to exenatide plus metformin. Although the proportion of patients reporting documented symptomatic hypoglycaemia with blood glucose < 50 mg/dl was similar in the add-on glimepiride (1/74; 1.4%) or TZD (1/76; 1.3%) groups, the exposure-adjusted mean rate/year was higher in the glimepiride group (0.10 vs 0.01 events/year of patient exposure).</p> <p>Secondary: Not reported</p>
<p>Zinman et al.⁵⁴ (2007)</p> <p>Exenatide 5 μg BID for 4 weeks followed by 10 μg BID</p>	<p>MC, PC, RCT</p> <p>Type 2 diabetics 21 to 75 years of age with a stable dose of a TZD (rosiglitazone ≥ 4 mg/day or</p>	<p>N=233</p> <p>16 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, body weight, self-monitored blood glucose</p>	<p>Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-0.89 ± 0.09 vs $0.09 \pm 0.10\%$; $P < 0.001$).</p> <p>Secondary: Exenatide significantly decreased FPG compared to placebo (-1.59 ± 0.22 vs 0.10 ± 0.21 mmol/L; $P < 0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs placebo</p> <p>All patients received existing TZD regimen, with or without metformin.</p>	<p>pioglitazone ≥ 30 mg/day) for ≥ 4 months before screening, alone or in combination with a stable dose of metformin for 30 days, HbA_{1c} 7.1 to 10.0%, BMI 25 to 45 kg/m², and a history of stable body weight ($\leq 10\%$ variation) for ≥ 3 months before screening</p>		<p>concentrations, safety</p>	<p>Exenatide significantly decreased weight compared to placebo (treatment difference, -1.51 kg; P<0.001).</p> <p>Exenatide-treated patients achieved significantly decreased self-monitored blood glucose profiles at each measurement throughout the day at week 16 compared to baseline (P<0.001) and placebo treated patients (P<0.001).</p> <p>Adverse events that were reported more commonly with exenatide included nausea (39.7 vs 15.2%; 95% CI, 12.7 to 36.3), vomiting (13.2 vs 0.9%; 95% CI, 5.2 to 19.5), and dyspepsia (7.4 vs 0.9%; 95% CI, 0.7 to 12.4).</p>
<p>Ratner et al.⁵⁵ (2006)</p> <p>Exenatide 5 μg SC BID for 4 weeks, followed by 10 μg SC BID</p> <p>All patients also received existing metformin therapy.</p>	<p>ES, MC, OL</p> <p>Type 2 diabetic patients 19 to 78 years of age, treated with metformin ($\geq 1,500$ mg/day) for ≥ 3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m², HbA_{1c} 7.1 to 11.0%, stable weight ($\pm 10\%$) for 3 months prior to screening, and no lab value >25% outside of normal value</p>	<p>N=150</p> <p>52 weeks (82 weeks total)</p>	<p>Primary: Changes in baseline HbA_{1c}, body weight, and lipid profile of the completer cohort (those patients who completed 82 weeks of exenatide) and total cohort (ITT population)</p> <p>Secondary: Proportion of patients in the completer cohort with baseline HbA_{1c} >7.0% who achieved an HbA_{1c} $\leq 7.0\%$, reduction of weight after stratification by baseline BMI, safety</p>	<p>Primary: At week 30, the completer cohort had significant decreases in HbA_{1c} from baseline of $-1.0 \pm 0.1\%$. At week 82, the decrease was $-1.3 \pm 0.1\%$ (95% CI, -1.5 to -1.0; P<0.05). For the total cohort, the decrease at week 30 was $-0.7 \pm 0.1\%$ (95% CI, -0.8 to -0.5; P<0.05) and at week 82 was $-0.8 \pm 0.1\%$ (95% CI, -1.0 to -0.6; P<0.05).</p> <p>At week 30, the completer cohort had significant decreases in body weight from baseline of -3.0 ± 0.6 kg. At week 82, the decrease from baseline was -5.3 ± 0.8 kg (95% CI, -7.0 to -3.7; P<0.05). For the total cohort, the decrease at week 30 was -2.3 ± 0.4 kg and at week 82 was -4.3 ± 0.6 kg (95% CI, -5.5 to -3.2; P<0.05).</p> <p>At week 82, the completer cohort experienced significant decreases in apo B (-5.20 mg/dL; 95% CI, -10.00 to -0.22; P value not reported), a reduction in TG (-73 mg/dL; 95% CI, -107 to -39; P value not reported) and an increase in HDL-C (4.5 mg/dL; 95% CI, 2.3 to 6.6; P value not reported).</p> <p>Secondary: At weeks 30 and 82, the proportion of patients in the completer cohort whose baseline HbA_{1c} was >7.0% and who achieved an HbA_{1c} $\leq 7.0\%$ was 46 and 59% (P values were not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Patients in the completer cohort whose baseline BMI ≥ 30 kg/m² experienced a greater decrease of weight (-6.9\pm1.1 kg) compared to those whose baseline BMI was <30 kg/m² (-2.3\pm0.8 kg; P values were not reported).</p> <p>The following adverse events were experienced by patients in the total cohort: nausea (14 to 33%), upper respiratory tract infections (3 to 10%), diarrhea (3 to 7%), vomiting (1 to 5%), and dizziness (2 to 6%) (P values were not reported).</p>
<p>Riddle et al.⁵⁶ (2006)</p> <p>Exenatide 5 μg SC BID or exenatide 5 μg SC BID for 4 weeks, followed by 10 μg SC BID</p> <p>All patients also received existing metformin and sulfonylurea therapies.</p>	<p>ES, MC, OL</p> <p>Type 2 diabetic patients 19 to 78 years of age, treated with metformin ($\geq 1,500$ mg/day) or maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥ 3 months before screening, FPG <240 mg/dL, BMI of 27 to 45 kg/m², HbA_{1c} 7.1 to 11.0%, stable weight ($\pm 10\%$) for 3</p>	<p>N=401</p> <p>52 weeks (82 weeks total)</p>	<p>Primary: Change in baseline HbA_{1c} and FPG in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population)</p> <p>Secondary: Change in baseline weight, change in baseline HbA_{1c} and weight stratified by baseline HbA_{1c} and BMI</p>	<p>Primary: At week 30, the completer cohort experienced a significant decrease in HbA_{1c} of -0.8\pm0.1% for the original exenatide 5 μg arm and -1.0\pm0.1% for the original 10 μg arm. At week 82, the decrease was -1.0\pm0.1% (95% CI, -0.9 to -1.2; P value not reported). For the total cohort group, the decrease at week 82 was -0.7\pm0.1% (95% CI, -0.8 to -0.5; P value not reported). Results from week 30 week were not reported.</p> <p>At week 30, the completer cohort observed a decrease in FPG of -0.52\pm0.16 mmol/L (P value not reported). At week 82, the decrease was -0.62\pm0.19 mmol/L (P value not reported). FPG data for the total cohort were not reported.</p> <p>Secondary: At week 30, the completer cohort group experienced a decrease in body weight of -1.4\pm0.3 kg for the original exenatide 5 μg arm and -2.1\pm0.3 kg for the original 10 μg arm. At week 82, the decrease was -4.0\pm0.3 kg (95% CI, -4.6 to -3.4). The total cohort experienced a decrease in body weight of -3.3\pm0.2 kg (95% CI, -2.8 to -3.7; P value not reported).</p> <p>At week 82, patients in the completer cohort who had a baseline BMI ≥ 30 kg/m² experienced a greater decrease in mean weight from baseline of -4.4\pm0.4 kg compared to -3.2\pm0.5 kg in patients with a baseline BMI <30 kg/m² (P values not reported).</p> <p>Of the patients in the completer cohort who had a baseline HbA_{1c} >7.0%, 44% achieved an HbA_{1c} $\leq 7.0\%$ at week 82. Patients with a baseline HbA_{1c} $\geq 9.0\%$ experienced a greater decrease (-1.9\pm0.2%) compared to those with a baseline HbA_{1c} <9.0% (-0.7\pm0.1%) (P values were not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	months prior to screening, and no lab value >25% outside of normal value			The most common reasons for withdrawal were administrative (study site closure) (12%), withdrawal of consent (11%), and adverse events (7%) (P values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 27% and 8 to 15% of patients, respectively (P values not reported).
<p>Blonde et al.⁵⁷ (2006)</p> <p>Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID</p> <p>All patients also received existing metformin and sulfonylurea therapies.</p>	<p>IA, MC, OL</p> <p>Type 2 diabetics</p>	<p>N=551</p> <p>52 weeks (82 weeks total)</p>	<p>Primary: Change in baseline HbA_{1c} and safety in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population)</p> <p>Secondary: Change in baseline FPG and weight, change in baseline weight and HbA_{1c} stratified by baseline BMI and HbA_{1c}, change in lipid profile</p>	<p>Primary: At week 30, the completer cohort experienced a significant decrease in HbA_{1c} of $-0.9 \pm 0.1\%$, and this decrease was maintained at week 82, with a decrease of $-1.1 \pm 0.1\%$ (95% CI, -1.0 to -1.3; P value not reported). The total cohort experienced a decrease at week 82 of $-0.8 \pm 0.1\%$ (95% CI, -0.6 to -0.9; P value not reported).</p> <p>Of the 551 ITT population, 314 (57%) patients completed the ES. Reasons for withdrawal included withdrawal of consent (11%), adverse events (7%), loss of glucose control (4%), and other (21%) (P values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 29% and 7 to 12% of patients, respectively (P values not reported).</p> <p>Secondary: At week 30, the completer cohort experienced a decrease in FPG of -0.7 ± 0.1 mmol/L (P value not reported). At week 82, the decrease was -0.9 ± 0.2 mmol/L (P value not reported). The total cohort FPG levels were not reported.</p> <p>At week 30, the completer cohort group experienced a decrease in body weight of -2.1 ± 0.2 kg and at week 82 the decrease was -4.4 ± 0.3 kg (95% CI, -3.8 to -5.1; P value not reported). At week 82, the total cohort experienced a decrease in body weight of -3.5 ± 0.2 kg (95% CI, -3.1 to -4.0; P value not reported).</p> <p>At week 82, patients in the completer cohort who had a baseline BMI ≥ 40 kg/m² experienced a decrease of -7 kg compared to -2 kg in patients with a baseline BMI < 25 kg/m² (P values not reported).</p> <p>In the completer cohort, of those patients whose baseline HbA_{1c} was $> 7.0\%$, 39 and 48% achieved HbA_{1c} $\leq 7.0\%$ at weeks 30 and 82, respectively. At week 82, a greater decrease in HbA_{1c} was achieved in patients who had a baseline HbA_{1c} $\geq 9.0\%$ (-2.0 ± 0.2) compared to those with a baseline HbA_{1c}</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p><9.0% (-0.8±0.1) (P values were not reported).</p> <p>In the completer cohort, of the lipid levels measured, significant benefits were observed in HDL-C (4 mg/dL; 95% CI, 3.7 to 5.4) and TG (-38.6 mg/dL; 95% CI, -55.5 to -21.6) at week 82 (P values not reported).</p>
<p>Buse et al.⁵⁸ (2007)</p> <p>Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID</p> <p>All patients also received existing metformin and sulfonylurea therapies.</p>	<p>IA, OL</p> <p>Type 2 diabetics</p>	<p>N=521</p> <p>104 weeks (2 years total)</p>	<p>Primary: Change in baseline HbA_{1c}, weight, and hepatic biomarkers; safety</p> <p>Secondary: Not reported</p>	<p>Primary: At week 104, exenatide significantly decreased HbA_{1c} by -1.1% (95% CI, -1.3 to -1.0; P<0.001).</p> <p>At week 104, exenatide significantly decreased weight by -4.7 kg (95% CI, -5.4 to -4.0; P<0.001).</p> <p>At Week 104, exenatide significantly decreased ALT by -5.3 IU/L (95% CI, -7.1 to -3.5; P<0.05) and decreased AST by -2.0 IU/L (95% CI, -3.3 to -0.8; P<0.05).</p> <p>Adverse events with an overall incidence ≥10% during 104 weeks of treatment were reported with the following proportion of patients affected: nausea (8 to 39%), upper respiratory tract infections (2 to 10%), and hypoglycemia (<1 to 13%) (P values were not reported).</p> <p>Secondary: Not reported</p>
<p>Klonoff et al.⁵⁹ (2008)</p> <p>Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID</p> <p>All patients also received existing metformin and sulfonylurea therapies.</p>	<p>IA, OE, OL</p> <p>Type 2 diabetics</p>	<p>N=217</p> <p>156 weeks (3 years total)</p>	<p>Primary: Change in baseline HbA_{1c}, weight, and ALT; safety</p> <p>Secondary: Not reported</p>	<p>Primary: At Week 156, exenatide significantly decreased HbA_{1c} by -1.0±0.1% (P<0.0001).</p> <p>At Week 156, exenatide significantly decreased weight by -5.3±0.4 kg (P<0.0001).</p> <p>At Week 156, exenatide significantly decreased ALT by -10.4±1.5 IU/L in patients with elevated ALT at baseline (P<0.0001).</p> <p>The most frequently reported adverse event was mild to moderate nausea.</p> <p>Secondary: Not reported</p>
Viswanathan et	RETRO	N=52	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>al.⁶⁰ (2007)</p> <p>Exenatide 5 µg SC BID</p> <p>vs</p> <p>control group (patients who discontinued exenatide therapy within 2 weeks on initiation due to insurance-related, personal or economic reasons)</p> <p>The dosages of rapid-acting and mixed insulin were reduced by 10% in patients with HbA_{1c} <7.5%.</p> <p>Subsequent dosage adjustments were made carefully based on ambient glucose concentrations.</p>	<p>Obese type 2 diabetic patients not adequately controlled despite treatment with oral hypoglycemic agents and insulin and HbA_{1c} >7.0%</p>	<p>26 weeks</p>	<p>Change in baseline body weight, HbA_{1c}, and insulin dose</p> <p>Secondary: Change in baseline TC, TG, DBP, SBP, and high-sensitivity CRP; safety</p>	<p>Exenatide-treated patients experienced a significant decrease in body weight of -6.46±0.80 kg (P<0.001) compared to the patients in the control group who experienced a significant weight gain of 2.4±0.6 kg (P<0.001).</p> <p>Exenatide-treated patients experienced a decrease in HbA_{1c} (-0.60±0.21%; P=0.007). The patients in the control group also experienced a decrease in HbA_{1c} (-8.4±0.5%; P value not reported).</p> <p>Exenatide-treated patients experienced a significant decrease in rapid-acting insulin requirements from 50.4±6.7 to 36.6±5.1 units (P<0.02) and for mixed insulin from 72.9±15.6 to 28.3±14.8 units (P<0.02). Insulin requirements for the control group were not reported.</p> <p>Secondary: Exenatide-treated patients experienced a significant decrease in TC from 163.9±8.2 to 149.8±5.9 mg/dL (P=0.03) compared to the patients in the control group who experienced a decrease from 168.1±16.3 to 144.33±10.39 mg/dL (P=0.08).</p> <p>Exenatide-treated patients experienced a significant decrease in TG from 202.5±28.8 to 149.9±17.3 mg/dL (P=0.01) compared to the patients in the control group who experienced a decrease from 182.7±23.9 to 171.1±39.2 mg/dL (P=0.91).</p> <p>Exenatide-treated patients experienced a significant decrease in SBP of -9.2±3.3 mm Hg (P=0.02). Data for the control group were not reported. Neither group experienced a reduction in DBP.</p> <p>Exenatide-treated patients experienced a significant decrease in high-sensitivity CRP of -34.0±14.3% (P=0.05). Data for the control group were not reported.</p> <p>Four patients receiving exenatide experienced severe nausea during treatment which led to discontinuation. Mild nausea was experienced by several other patients that did not interfere with therapy. Hypoglycemia (glucose <60 mg/dL) was rare and did not lead to any hospital admissions. No other adverse events were observed.</p>
<p>Grimm et al.⁶¹</p>	<p>MA (post-hoc)</p>	<p>N=1,379</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2013)</p> <p>Exenatide once weekly</p>	<p>(DURATION 1 through 6 trials)</p> <p>Patients with type 2 diabetes, age ≥ 16 years, baseline HbA_{1c} level of 7.1% to 11%, a history of stable body weight, and a BMI ≤ 45 kg/m²</p>	<p>24 to 30 weeks</p>	<p>Effects of 24 to 30 weeks of treatment with weekly exenatide on glycemic control, body weight, and CV risk factors</p> <p>Secondary: Not reported</p>	<p>At the end of the 24 to 30 week assessment period, 59% of population (compared with 3% at baseline) had achieved an HbA_{1c} level $<7\%$, and 39% (compared with $<1\%$ at baseline) had achieved an HbA_{1c} level $\leq 6.5\%$. FPG levels also progressively declined over time and were significantly reduced at endpoint. Modest but significant reductions in CV risk factors, including BP and fasting lipid levels, were observed following 24 to 30 weeks of exenatide once weekly treatment. Treatment with exenatide was also associated with progressive reductions in body weight. Patients experienced a least-squares mean reduction (95% CI) in body weight of -2.5 kg (-2.8 to -2.3 kg) at endpoint. At endpoint, 76% of the population experienced weight loss.</p> <p>Secondary: Not reported</p>
<p>Marre et al.⁶² (2009)</p> <p>LEAD-1</p> <p>Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo</p> <p>vs</p> <p>placebo plus glimepiride 2 to 4 mg/day</p> <p>vs</p> <p>placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day</p>	<p>AC, DB, DD, MC, PG, RCT</p> <p>Type 2 diabetic patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥ 3 months, HbA_{1c} 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤ 45 kg/m²</p>	<p>N=1,041</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients reaching HbA_{1c} (<7.0 and $\leq 6.5\%$), FPG (5.0 to ≤ 7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP</p>	<p>Primary: After 26 weeks, HbA_{1c} decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; $P<0.0001$); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; $P<0.0001$); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; $P<0.0001$); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; $P<0.0001$). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were more efficacious compared to treatment with rosiglitazone ($P<0.0001$ for both measures). Decreases in HbA_{1c} were greater in patients previously on an oral glucose lowering agent monotherapy.</p> <p>Secondary: The proportion of patients reaching HbA_{1c} targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached HbA_{1c} <7.0 and $\leq 6.5\%$ compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching HbA_{1c} targets were greater compared to patients receiving placebo ($P<0.0001$) and rosiglitazone ($P<0.0003$), respectively. More patients reached $<7.0\%$ with liraglutide 1.8 mg compared to 1.2 mg ($P=0.018$).</p> <p>The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; $P=0.002$), 1.2 mg (37%; $P<0.001$), and 1.8 mg (38%; $P=0.002$) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively).</p> <p>The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported).</p> <p>Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported).</p> <p>Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR.</p> <p>Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported).</p>
<p>Nauck et al.⁶³ (2009) LEAD-2</p> <p>Liraglutide 0.6, 1.2, and 1.8 mg SC QD</p> <p>vs</p> <p>placebo</p> <p>vs</p> <p>glimepiride 4 mg/day</p>	<p>AC, DB, DD, MC, PG, RCT</p> <p>Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy ≥3 months), and BMI ≤40 kg/m²</p>	<p>N=1,091</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Changes in baseline body weight, FPG, seven-point self-monitored glucose concentrations, and β cell function</p>	<p>Primary: HbA_{1c} decreased by -0.7±0.1% with liraglutide 0.6 mg, -1.0±0.1% with liraglutide 1.2 and 1.8 mg, and increased by 0.1±0.1% with glimepiride and placebo. Based on the estimated treatment differences, liraglutide had more efficacious glycemic control compared to placebo (liraglutide 0.6 mg vs placebo, -0.8%; 95% CI, -1.0 to -0.6 and liraglutide 1.2 and 1.8 mg vs placebo, -1.1%; 95% CI, -1.3 to -0.9; P values not reported). Analysis of the estimated treatment difference in HbA_{1c} between liraglutide and glimepiride demonstrated that liraglutide 1.2 and 1.8 mg were noninferior to treatment with glimepiride.</p> <p>Secondary: Weight loss was dose-dependent with liraglutide (liraglutide 0.6 mg, -1.8±0.2 kg; liraglutide 1.2 mg, -2.6±0.2 kg; liraglutide 1.8 mg, -2.8±0.2 kg). Reductions in weight with liraglutide were significantly different compared to glimepiride (-1.0±0.2 kg; P<0.001). Weight loss with liraglutide 1.2 and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>All patients also received metformin 1,500 to 2,000 mg/day.</p>				<p>1.8 mg was significantly greater compared to placebo (1.5±0.3 kg; P≤0.01).</p> <p>Decreases in FPG with liraglutide (-1.1, -1.6, and -1.7 mmol/L with liraglutide 0.6, 1.2, and 1.8 mg) were significantly greater compared to the increase with placebo (0.4 mmol/L; P<0.0001). Decreases with liraglutide were similar to glimepiride (-1.3 mmol/L; P value not reported).</p> <p>Mean baseline PPG values decreased with all liraglutide doses and glimepiride (liraglutide 0.6 mg, -1.7 mmol/L; liraglutide 1.2 mg, -2.3 mmol/L; liraglutide 1.8 mg, -2.6 mmol/L; glimepiride, -2.5 mmol/L; placebo, -0.6 mmol/L; P<0.001 for comparisons of all liraglutide doses vs placebo). The decreases observed with liraglutide 1.2 and 1.8 mg were comparable to glimepiride (P values not reported).</p> <p>No differences in the fasting C-peptide values were observed between liraglutide and glimepiride or placebo (P values not reported).</p> <p>Decreases in the proinsulin: insulin ratio with all three liraglutide doses (-0.1) were comparable to glimepiride (P value not reported), and were significantly greater compared to placebo (0.1; P<0.0001).</p> <p>Liraglutide 0.6, 1.2, and 1.8 mg had improvements in HOMA-B of 63, 70, and 71%. Glimepiride had similar improvements, and there were no improvements with placebo. No differences were observed between any of the treatments (P values not reported).</p>
<p>Zinman et al.⁶⁴ (2009) LEAD-4</p> <p>Liraglutide 1.2 and 1.8 mg SC QD</p> <p>vs</p> <p>placebo</p> <p>All patients also received</p>	<p>DB, MC, PC, PG, RCT</p> <p>Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering</p>	<p>N=533</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline body weight, FPG, seven-point self-monitored glucose concentrations, β cell function, and lipids</p>	<p>Primary: The mean baseline HbA_{1c} for the overall population decreased by -1.5±0.1% with liraglutide 1.2 (95% CI, -1.1 to -0.8; P value not reported) and 1.8 mg (95% CI, -1.1 to -0.8; P value not reported) compared to -0.5±0.1% with placebo.</p> <p>Secondary: Weight loss with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -1.0±0.3 kg and liraglutide 1.8 mg, -2.0±0.3 kg; P<0.0001 for both).</p> <p>Decreases in FPG with liraglutide (liraglutide 1.2 mg, -2.2 mmol/L and liraglutide 1.8 mg, -2.4 mmol/L) were significantly greater compared to</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 2,000 mg/day and rosiglitazone 8 mg/day.	agent combination therapy for ≥ 3 months), and BMI ≤ 45 kg/m ²			<p>placebo (-0.4 mmol/L; P<0.0001 for both).</p> <p>Decreases in mean PPG were significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, -2.6 mmol/L; liraglutide 1.8 mg, -2.7 mmol/L; and placebo, -0.8 mmol/L; P<0.001 for both).</p> <p>The decrease in proinsulin:insulin ratio with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -0.029±0.026; liraglutide 1.8 mg -0.085±0.260; placebo, 0.036±0.029; P<0.05 for both).</p> <p>The increase in C-peptide was significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, 131±32; liraglutide 1.8 mg, 144±31; placebo, 51±34 pmol/L; P<0.05 for both).</p> <p>Increases in HOMA-B with liraglutide were significantly greater compared to placebo (P<0.05), but decreases with HOMA-IR were not different between treatments (P values not reported).</p> <p>Decreases in FFA were significantly greater with liraglutide 1.2 mg (-0.03±0.02 mmol/L; P<0.05) and liraglutide 1.8 mg (-0.05±0.02 mmol/L; P<0.05) compared to placebo (0.02±0.02). Other significant decreases in lipid profiles with liraglutide compared to placebo were LDL-C (liraglutide 1.2 mg, -0.28±0.07 vs -0.10±0.07 mmol/L; P<0.05) and TG (liraglutide 1.2 mg, -0.38±0.10 vs -0.13±0.11 mmol/L; P<0.05).</p>
<p>Marso et al.⁶⁵ (2016) LEADER</p> <p>Liraglutide 1.8 mg SC QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, RCT</p> <p>Patients ≥ 50 years of age with type 2 diabetes with at least one cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney</p>	<p>N=9,340</p> <p>Median follow-up of 3.8 years</p>	<p>Primary: First occurrence of death from cardiovascular causes, nonfatal (including silent myocardial infarction, or nonfatal stroke</p> <p>Secondary: Not reported</p>	<p>Primary: The primary composite outcome occurred in fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (HR, 0.87; 95% CI, 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III) or an age of 60 years or more with at least one cardiovascular risk factor, as determined by the investigator			
<p>Russell-Jones et al.⁶⁶ (2009) LEAD-5</p> <p>Liraglutide 1.8 mg SC QD</p> <p>vs</p> <p>placebo</p> <p>vs</p> <p>insulin glargine (OL)</p> <p>All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day.</p>	<p>PC, PG, RCT</p> <p>Type 2 diabetic patients 18 to 80 years of age with oral glucose lowering agents ≥ 3 months before screening, HbA_{1c} 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination therapy), and BMI ≤ 45 kg/m²</p>	<p>N=581</p> <p>26 weeks</p>	<p>Primary: Change in baseline in HbA_{1c}</p> <p>Secondary: Change in baseline body weight, waist circumference, FPG, eight-point self-monitored glucose concentrations, β cell function, and BP</p>	<p>Primary: Decreases in HbA_{1c} were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -1.09%; 95% CI, -1.28 to -0.90; P<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; P=0.0015).</p> <p>Secondary: The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; P=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; P<0.0001).</p> <p>The decrease in waist circumference with liraglutide (-1.50 cm) was significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; P<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; P=0.0608).</p> <p>Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; P<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin (-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; P<0.0001), but not compared to insulin (data not reported).</p> <p>Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, -0.00366; 95% CI, -0.00597 to -0.00136; P=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; P<0.0001) were achieved with liraglutide.</p> <p>A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; P=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; P=0.0791). No significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin.</p>
<p>Kaku et al.⁶⁷ (2010)</p> <p>Liraglutide 0.6 and 0.9 mg SC QD</p> <p>vs</p> <p>placebo</p> <p>All patients received existing sulfonylurea therapy.</p>	<p>DB, MC, PG, RCT</p> <p>Japanese type 2 diabetics ≥ 20 years of age currently treated with a sulfonylurea for ≥ 8 weeks, HbA_{1c} 7.0 to <10.0%, and BMI <35 kg/m²</p>	<p>N=264</p> <p>52 weeks (initial 24 week DB period, followed by 28 week OL period to assess the long-term safety and efficacy of liraglutide)</p>	<p>Primary: Change in baseline HbA_{1c} at 24 weeks</p> <p>Secondary: seven-point self-monitored glucose concentrations, body weight, FPG, PPG, lipid profile, biomarkers for cardiovascular effects, proportion of patients reaching an HbA_{1c} <7.0 or <6.5% (post-hoc analysis)</p>	<p>Primary: Liraglutide significantly decreased and sustained HbA_{1c} compared to placebo. The decrease at week 24 was greater with liraglutide 0.9 mg (-1.56\pm0.84%) compared to the other treatments (liraglutide 0.6 mg, -1.46\pm0.95% and placebo, -0.40\pm0.93%). HbA_{1c} at week 24 were significantly lower with liraglutide compared to placebo (7.02 and 6.75% with liraglutide 0.6 and 0.9 mg compared to 8.02% with placebo) with the treatment differences of -1.00% (95% CI, -1.24 to -0.75) with liraglutide 0.6 mg and -1.27% (95% CI, -1.51 to -1.02) with liraglutide 0.9 mg.</p> <p>Secondary: Improvements in metabolic controls were apparent in the seven-point self monitored glucose concentration profiles at week 24, with significant reductions in glucose. Plasma glucose was significantly lower with liraglutide compared to placebo (P<0.0001).</p> <p>Body weight did not change with liraglutide (0.6 mg, 0.06 kg and 0.9 mg, -0.37 kg) despite the improvements seen in glycemic control (P values not reported). Weight decreased with placebo (-1.12 kg).</p> <p>Full impact on FPG levels was achieved at the first two visits at week four,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>and levels were significantly lower with liraglutide at week 24 compared to placebo. FPG with liraglutide 0.6 and 0.9 mg was significantly lower compared to placebo (7.34±0.19, 7.01±0.19, and 8.81±0.19 mmol/L, respectively; P<0.0001). The estimated means of PPG at week 24 at all time points with liraglutide were lower compared to placebo, with much lower mean values occurring with liraglutide 0.9 mg (P values not reported). The means of AUC_{0-3hr} at week 24 were also significantly lower with liraglutide compared to placebo (P<0.0001).</p> <p>No significant treatment effects were observed in any of the parameters of the lipid profile. The cardiovascular biomarker BNP was significantly lower with liraglutide compared to placebo (liraglutide 0.6 mg vs placebo; P=0.0018 and liraglutide 0.9 mg vs placebo; P=0.0157). High-sensitivity CRP was significantly lower with liraglutide 0.6 mg compared to placebo (P=0.0218), but no difference was observed between liraglutide 0.9 mg and placebo (P=0.8143). No treatment effect was seen in the estimated mean of PAI-1 at week 24 (P values not reported).</p> <p>A significantly greater proportion of patients receiving liraglutide achieved HbA_{1c} values <7.0 and <6.5% compared to placebo (P values not reported).</p>
<p>Ahmann et al.⁶⁸ (2015)</p> <p>Liraglutide 1.8 mg SC QD</p> <p>vs</p> <p>placebo</p> <p>added to their pre-existing basal insulin analogue (≥20 U/day) ± metformin (≥1500 mg/day)</p>	<p>DB, MC, RCT</p> <p>Adults with inadequately controlled type 2 diabetes (HbA_{1c} of 7.0 to 10.0%)</p>	<p>N=451</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: HbA_{1c} <7 or ≤6.5%, FPG, seven-point self-measured plasma glucose values, body weight, SBP, adverse events</p>	<p>Primary: After 26 weeks of treatment, HbA_{1c} was reduced more with liraglutide than with placebo (-1.3 vs -0.1%), with an estimated treatment difference of -1.2% (95% CI, -1.4 to -1.0%; P<0.0001).</p> <p>Secondary: More subjects on liraglutide reached HbA_{1c} targets: <7.0% (59 vs 14%; P<0.0001) and ≤6.5% (43 vs 4%; P<0.0001) using slightly less insulin (35.8 vs 40.1 IU). Greater decreases from baseline (estimated treatment differences vs placebo; P<0.0001) occurred in fasting plasma glucose (-1.3 mmol/l), seven-point glucose profiles (-1.6 mmol/l), body weight (-3.1 kg) and systolic blood pressure (-5.0 mmHg). Transient gastrointestinal adverse events (nausea: 22.2 vs 3.1%) and minor hypoglycaemia (18.2 vs 12.4%) were more frequent with liraglutide than placebo, and pulse increased (4.5 beats/min) compared with placebo. No severe hypoglycaemia or pancreatitis occurred.</p>
<p>Drucker et al.⁶⁹ (2008)</p>	<p>AC, OL, NI, RCT</p>	<p>N=303</p>	<p>Primary: Change in baseline</p>	<p>Primary: Both treatments achieved significant decreases in HbA_{1c}, with a decrease at</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>DURATION-1</p> <p>Exenatide ER 2 mg SC once weekly</p> <p>vs</p> <p>exenatide 5 µg SC BID for 28 days, followed by 10 µg BID</p>	<p>Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m²; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents</p>	<p>30 weeks</p>	<p>HbA_{1c}</p> <p>Secondary: Safety and tolerability; FPG and PPG; body weight; fasting glucagon; fasting lipids; BP; proportion of patients achieving HbA_{1c} ≤7.0, ≤6.5, and ≤6.0%; exenatide antibodies</p>	<p>week 30 of -0.33±0.10% (95% CI, -0.54 to -0.12). Decreases were significantly greater with exenatide ER compared to exenatide (-1.9±0.1 vs -1.5±0.1%; P=0.0023). Significant decreases with both treatments were observed as early as week six, and the mean decrease was significantly greater with exenatide ER compared to exenatide by week 10, and the difference persisted throughout the remainder of the trial. Overall, decreases were consistent across all treatment background therapies and did not vary notably with sex or age (>65 years vs <65 years).</p> <p>Secondary:</p> <p>Adverse events reported in >10% of patients include nausea (26.4 vs 34.5%), vomiting (10.8 vs 18.6%), injection site pruritus (17.6 vs 1.4%), upper respiratory tract infection (8.1 vs 17.2%), diarrhea (13.5 vs 13.1%), constipation (10.8 vs 6.2%), injection site bruising (4.7 vs 10.3%), and urinary tract infection (10.1 vs 8.3%). Gastrointestinal complaints were the most frequently reported adverse events with exenatide. Treatment-related nausea was reported in significantly fewer patients receiving exenatide ER (P value not reported). Reported nausea with both treatments was predominantly mild in intensity, and no severe nausea was reported with exenatide ER. Injection site pruritus with either treatment was typically mild in intensity, and resolved with continued treatment. No episodes of major hypoglycemia were reported with either treatment, and the incidence of minor hypoglycemia was low. Withdrawals due to adverse events were 6.1 vs 4.8% (P value not reported). No clinically significant abnormalities in vital signs; electrocardiogram reports; or hematological, chemistry, or urinalysis values were reported. The incidence of serious adverse events was low (5.4 vs 3.4%). No cases of pancreatitis were reported with either treatment.</p> <p>Both treatments achieved significant decreases in FPG and PPG, with exenatide ER achieving significantly greater decreases in FPG compared to exenatide (-2.3±0.2 vs -1.4±0.2 mmol/L; 95% CI, -1.3 to -5.2; P<0.0001). Analysis across all background treatments revealed similar results. Similar results were observed with PPG (data reported in graphical form only). Both treatments resulted in significant improvements in 7-point self-monitored glucose concentrations profiles.</p> <p>Body weight decreased progressively with both treatments (-3.7±0.5 vs -3.6±0.5 kg; 95% CI, -1.3 to 1.1; P=0.89). At week 30, the mean percentage of</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>weight loss from baseline was -3.6 vs -3.7% with exenatide ER and exenatide (P>0.05).</p> <p>Both treatments significantly decreased FPG and PPG (P values not reported).</p> <p>Exenatide ER achieved significantly greater decreases in TC (-0.31±0.06 vs -0.10±0.06 mmol/L) and LDL-C (-0.13±0.05 vs 0.03±0.05 mmol/L) compared to exenatide (P values not reported). TG decreased with both treatments (-15 vs -11%; P value not reported).</p> <p>Both treatments achieved significant improvements in SBP and DBP (P values not reported).</p> <p>A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} ≤7.0% compared to patients receiving exenatide (77 vs 61%; P=0.0039). Forty nine and 25% of patients receiving exenatide ER achieved HbA_{1c} ≤6.5 and ≤6.0%.</p> <p>Anti-exenatide antibody levels were significantly higher with exenatide ER compared to exenatide (P=0.0002), but most antibodies were either not detectable or of low titer.</p>
<p>Buse et al.⁷⁰ (2010) DURATION-1</p> <p>Exenatide ER 2 mg SC once weekly (continued exenatide ER)</p> <p>vs</p> <p>exenatide ER 2 mg SC once weekly (switched to exenatide ER)</p>	<p>ES (DURATION-1⁴⁴)</p> <p>Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m²; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD,</p>	<p>N=258</p> <p>22 weeks (52 weeks total)</p>	<p>Primary: Efficacy, body weight, glucose control, lipid and BP profile, safety and tolerability</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>During the 22 weeks, patients who continued exenatide ER maintained improvements in HbA_{1c}, with a decrease of -2.1% (95% CI, -2.2 to -1.9) at week 30 and -2.0% (95% CI, -2.1 to -1.8) at week 52. Patients who switched to exenatide ER (week 30 HbA_{1c} decrease, -1.8%; 95% CI, -1.9 to -1.6) exhibited further improvements in glycemic control and achieved the same reduction (-2.0%) and mean HbA_{1c} (6.6%) at week 52 compared to patients who continued exenatide ER. After 52 weeks, 71 and 54% of all patients achieved an HbA_{1c} ≤7.0 and ≤6.5% (similar between the two cohorts). In patients with a baseline HbA_{1c} <9.0%, the decrease at week 52 was -1.2 (95% CI, -1.4 to -1.1) and -1.3% (95% CI, -1.5 to -1.2) in patients who continued exenatide ER and in those who switched to exenatide ER. Larger decreases in HbA_{1c} were observed in patients with a baseline HbA_{1c} ≥9.0% (-2.8 [95% CI, -3.1 to -2.5] vs -2.6% [95% CI, -3.0 to -2.3]).</p> <p>Body weight decreased similarly with both treatments. At week 52, the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Patients enrolled in DURATION-1 who were randomized to exenatide 10 µg SC BID were transitioned to exenatide ER 2 mg SC once weekly after the initial 30 week trial period.</p>	<p>or any combination of 2 of these agents</p>			<p>decreases in body weight were -4.1 (95% CI, -5.3 to -2.9) vs -4.5 kg (95% CI, -5.7 to -3.3) in patients who continued exenatide ER and those who switched to exenatide ER.</p> <p>In patients who continued exenatide ER, the decreases in FPG achieved at week 30 (-46 mg/dL; 95% CI, -52 to -40) were maintained throughout the 52 weeks (-47 mg/dL; 95% CI, -53 to -41). Patients who switched to exenatide ER achieved a similar decrease in FPG at week 52 (-43 mg/dL; 95% CI, -49 to -37). Subsequent to week 30, patients switched to exenatide ER experienced a transient rise in mean FPG followed by a rapid decreases within two weeks after switching treatment.</p> <p>Clinically significant improvements in BP were observed in patients who continued exenatide ER for 52 weeks. (SBP, -6.2 mm Hg; 95% CI, -8.5 to -3.9 and DBP, -2.8 mm Hg; 95% CI, -4.3 to -1.3) and in patients who switched to exenatide ER (SBP, -3.8 mm Hg; 95% CI, -6.1 to -1.5 and DBP, -1.8 mm Hg; 95% CI, -3.2 to -0.3). Fifty and 36% of patients in the two treatment groups who had elevated SBP at baseline achieved normal SBP at week 52. Improvements in lipid profiles were achieved in both treatment groups, with clinically significant decreased in TC (-9.6 [95% CI, -14.8 to -4.3] and -9.0 mg/dL [95% CI, -14.5 to -3.6]) and TG (-15%; 95% CI, -21 to -9).</p> <p>Treatment-emergent adverse events that occurred for the first time or worsened during the 22 week long second phase were similar to those observed during the initial 30 weeks of treatment. Nausea was predominantly mild, and no severe cases were reported. Twenty one patients (four vs 17) reported injection site-related adverse events. Mild to moderate injection site pruritus was observed after switching from exenatide to exenatide ER in six patients. No cases of pancreatitis were reported.</p> <p>Secondary: Not reported</p>
<p>Blevins et al.⁷¹ (2011) DURATION-5 Exenatide ER 2</p>	<p>AC, MC, OL, RCT Type 2 diabetics ≥18 years of age treated for ≥2</p>	<p>N=252 24 weeks</p>	<p>Primary: Change in baseline HbA_{1c} Secondary:</p>	<p>Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER compared to exenatide (-1.6±0.1 vs -0.9±0.1%, treatment difference, -0.7%; 95% CI, -0.9 to -0.4). At week 24, HbA_{1c} was 7.1±0.1 and 7.7±0.1% with exenatide ER and exenatide.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>mg SC once weekly</p> <p>vs</p> <p>exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID</p>	<p>months with diet and exercise alone or with a stable, maximally effective regimen of metformin, sulfonylurea, TZD, or a combination of these medications; HbA_{1c} 7.1 to 11.0%; FPG <280 mg/dL; and BMI 25 to 45 kg/m²</p>		<p>Proportion of patients achieving HbA_{1c} <7.0 and <6.5% and FPG ≤126 mg/dL, body weight, FPG, BP, lipid profile, safety and tolerability</p>	<p>Secondary:</p> <p>A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0 (58.1 vs 30.1%; P<0.0001) and <6.5% (41.1 vs 16.3%; P<0.0001) compared to exenatide. Similar results were achieved for FPG ≤126 mg/dL (50.4 vs 30.9%; P=0.0008).</p> <p>Both treatments resulted in progressive decreases in body weight through 24 weeks (between group difference, -0.95 kg; 95% CI, -1.9 to 0.01). By week 24, 77 and 63% of patients receiving exenatide ER and exenatide experienced weight loss, whereas 71 and 51% of patients experienced both weight loss and a decrease in HbA_{1c}.</p> <p>Decreases in FPG were significantly greater with exenatide ER compared to exenatide (-35±5 vs -12±5 mg/dL; P=0.0008).</p> <p>Decreases in SBP were significant with exenatide ER (-2.9±1.1 mm Hg; 95% CI, -5.2 to -0.7), but not with exenatide. No significant decreases in DBP were observed with either treatment.</p> <p>Decreases in TC (-15.4±2.6 mg/dL; 95% CI, -20.5 to -10.2) and LDL-C (-6.4±2.1 mg/dL; 95% CI, -10.7 to -2.2) were significant with exenatide ER, and no significant changes were observed with exenatide.</p> <p>Nausea, the adverse event most commonly reported with both treatments (14 vs 35%), occurred at a lower incidence in patients receiving exenatide ER. Injection site-related adverse events were more common with exenatide ER (13 vs 10%), with one patient receiving exenatide ER withdrawing from treatment due to mild injection site pruritus. There were no major hypoglycemic episodes. The incidences of serious adverse events were low (2 vs 4%). During the course of treatment there was substantial variability in pancreatic-amylase and lipase concentrations. The incidence of adverse events, including gastrointestinal symptoms was similar between patients with normal and abnormal post-baseline amylase and lipase measured at any post-baseline time point.</p>
<p>Buse et al.⁷² (2009) LEAD-6</p>	<p>AC, MC, OL, PG, RCT</p>	<p>N=464 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p>	<p>Primary: Decreases in HbA_{1c} with liraglutide were more efficacious compared to exenatide (-1.12 vs -0.79%; treatment difference, -0.33; 95% CI, -0.47 to -</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Liraglutide 1.8 mg SC QD</p> <p>vs</p> <p>exenatide 10 µg SC BID</p> <p>Background oral glucose-lowering agents were maintained at pre-trial doses unless unacceptable hypoglycemia occurred, in which case sulfonylurea doses could be reduced to no less than 50% of the starting dose.</p>	<p>Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m²; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months</p>		<p>Secondary: Proportion of patients reaching HbA_{1c} targets (<7.0 and ≤6.5%); change in baseline FPG, seven-point self-monitored glucose concentrations, body weight, β cell function, glucagon, BP, and lipid profiles</p>	<p>0.18; P value not reported). Data in the ITT population demonstrated similar decreases with liraglutide and exenatide (-1.16 vs -0.87%; estimated treatment difference, -0.29%; 95% CI, -0.45 to -0.13; P<0.0001).</p> <p>Secondary: The proportion of patients achieving target HbA_{1c} was significantly greater with liraglutide compared to exenatide (HbA_{1c} <7.0%, 54 vs 43%; OR, 2.02; 95% CI, 1.31 to 3.11; P value not reported and HbA_{1c} ≤6.5%, 35 vs 21%; OR, 2.73; 95% CI, 1.68 to 4.43; P value not reported).</p> <p>Significant decreases in FPG were achieved with liraglutide compared to exenatide (-1.61 vs -0.60 mmol/L; treatment difference, -1.01 mmol/L; 95% CI, -1.37 to -0.65; P<0.0001).</p> <p>In contrast, exenatide decreased PPG significantly more compared to liraglutide after breakfast (treatment difference, -1.33 mmol/L; 95% CI, 0.80 to 1.86; P<0.0001) and dinner (treatment difference, -1.01 mmol/L; 95% CI, 0.44 to 1.57; P=0.0005). After lunch differences between the two treatments were not significant (data not reported).</p> <p>Both treatments were associated with decreases in body weight (-3.24 vs -2.87 kg; treatment difference, -0.37 kg; 95% CI, -0.99 to 0.23; P=0.2235).</p> <p>Increases in HOMA-B were significant with liraglutide compared to exenatide (32.12 vs 2.74%; treatment difference, 29.38%; 95% CI, 16.81 to 41.93; P<0.0001).</p> <p>Decreases in fasting glucagon were not different between the two treatments (-19.44 vs -12.33 ng/L; treatment difference, -7.11 ng/L; 95% CI, -16.66 to 2.43; P=0.1436).</p> <p>No differences were observed between the two treatments in terms of decreases in SBP (P=0.6409) or DBP (P=0.1610).</p> <p>In terms of lipid profiles, significant changes favoring liraglutide were observed only for VLDL-C (P=0.0277), TG (P=0.0485), and FFA (P=0.0014). All other lipid parameters were similar between the two treatments.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Buse et al.⁷³ (2010)</p> <p>Liraglutide 1.8 mg SC QD (continued liraglutide)</p> <p>vs</p> <p>liraglutide 1.8 mg SC QD (switched to liraglutide)</p> <p>Patients enrolled in LEAD-6 who were randomized to exenatide 10 µg SC BID were transitioned to liraglutide 1.8 mg SC QD after the initial 26 week trial period.</p>	<p>ES (LEAD-6⁴⁷)</p> <p>Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m²; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months</p>	<p>N=376</p> <p>14 weeks (40 weeks total)</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, body weight, and SBP; adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: HbA_{1c} decreased further from 7.2% at week 26 to 6.9±0.32% at week 40 (P<0.0001) after switching from exenatide to liraglutide, but remained similar with continued liraglutide treatment (7.0 to 6.9±-0.06%; P=0.1222). Additional patients reached HbA_{1c} targets after switching from exenatide to liraglutide.</p> <p>After switching from exenatide to liraglutide, further decreases in FPG (-0.9±0.16 mmol/L; P<0.0001), body weight (-0.9±0.15 kg; P<0.0001), and SBP (-3.8±0.84 mmHg; P<0.0001) occurred, while HOMA-B increased (14.5±4.4%; P=0.001), consistent with FPG reductions. With continued liraglutide treatment, reductions in FPG (-0.2±0.11 mmol/L; P=0.0973), body weight (-0.4±0.15 kg; P=0.0089), and SBP (-2.2±0.88 mmHg; P=0.0128) occurred.</p> <p>No significant changes in PPG occurred in either treatment group (P value not reported).</p> <p>Similar numbers of patients reported one or more adverse events during the ES (37.6 vs 37.4%; P value not reported). Most adverse events were mild in severity. Nausea and diarrhea occurred in 1.5% of patients who continued liraglutide and 3.2% of patients who switched from exenatide to liraglutide, whereas vomiting occurred in 2.0% of patients who continued liraglutide and 0.5% of patients who switched from exenatide to liraglutide. One major hypoglycemic episode occurred in a patient continuing liraglutide. Four patients who switched from exenatide to liraglutide had seven severe adverse events (cardiac failure, MI, cataract, chest discomfort, COPD, and dyspnea). Five patients continuing liraglutide had eight severe adverse events (cerebral infarction, cerebrovascular accident, TIA, acute coronary syndrome, coronary artery occlusion, portal vein thrombosis, rectal cancer, and depression). Calcitonin levels remained at the lower level of the normal range (<1 pg/mL) and did not differ between treatment groups. No medullary thyroid carcinoma or pancreatitis cases were reported.</p> <p>Secondary: Not reported</p>
<p>Heine et al.⁷⁴ (2005)</p>	<p>OL, RCT</p>	<p>N=551</p>	<p>Primary: Change in HbA_{1c}</p>	<p>Primary: At 26 weeks, similar reductions in HbA_{1c} were noted between exenatide and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Exenatide 5 µg BID for 4 weeks, then 10 µg BID</p> <p>vs</p> <p>insulin glargine QD at bedtime</p> <p>All patients were receiving existing metformin and/or sulfonylurea regimens.</p>	<p>Patients 30 to 75 years of age with type 2 diabetes not adequately controlled (defined as HbA_{1c} 7.0 to 10.0%) with combination metformin and sulfonylurea therapy at maximally effective doses, BMI 25 to 45 kg/m² and a history of stable body weight (≤10% variation for ≥3 months before screening)</p>	<p>26 weeks</p>	<p>Secondary: Change in FPG, fasting glucose <100 mg/dL and body weight loss</p>	<p>insulin glargine (–1.11%, CI, –0.123 to 0.157).</p> <p>Secondary: A significantly reduction in FPG from baseline was observed in the insulin glargine group (–51.5 mg/dL; P<0.001). The reduction from baseline in the exenatide group was not significant (–25.7 mg/dL). A significant reduction was observed in the insulin group when compared to the exenatide group (95% CI, 20 to 34 mg/dL).</p> <p>A significantly greater proportion of patients taking insulin glargine (21.6%) achieved fasting glucose of <100 mg/dL than those taking exenatide (8.6%; P<0.001).</p> <p>A significant weight loss was experienced in the exenatide group (–2.3 kg) compared to a gain of +1.8 kg in the insulin group (CI, –4.6 to –3.5 kg; P<0.001).</p> <p>Similar rates of hypoglycemia were reported with both agents (CI, –1.3 to 3.4 events/patient-year). Exenatide patients had a higher incidence of daytime hypoglycemia (CI, 0.4 to 4.9 events/patient-year), and a lower rate of nocturnal hypoglycemia than insulin glargine patients (CI, –2.3 to –0.9 events/patient-year).</p> <p>A significantly higher incidence of gastrointestinal side effects, including nausea (57.1 vs 8.6%; P<0.001), vomiting (17.4 vs 3.7%; P<0.001) and diarrhea (8.5 vs 3%; P=0.006), upper abdominal pain (P=0.012), constipation (P=0.011), dyspepsia (P=0.011), decreased appetite (P=0.021), and anorexia (P=0.002) were reported in the exenatide group vs the insulin group.</p> <p>Withdrawals due to adverse events occurred in 9.5% of exenatide patients vs 0.7% of insulin patients.</p>
<p>Secnik Boye et al.⁷⁵ (2006)</p> <p>Exenatide 5 µg BID for 4 weeks, then 10 µg BID</p>	<p>MC, OL, RCT</p> <p>Secondary analysis on patients with type 2 diabetes inadequately controlled (defined</p>	<p>N=455</p> <p>26 weeks</p>	<p>Primary: Patient-reported health outcome measures: Diabetes Symptom Checklist-revised, DTSQ, EQ-5D,</p>	<p>Primary: Both exenatide and insulin glargine groups experienced a significant improvement from baseline in patient-reported health outcome measures as demonstrated by Diabetes Symptom Checklist-revised overall scores, DTSQ, EQ-5D and Medical Outcomes Study 36-Item Short-Form Health Survey scores (P<0.05 for all measures). There was not a statistical difference between treatment groups in any of the outcome measures (P>0.05 for all</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>insulin glargine QD at bedtime</p> <p>All patients were receiving existing metformin and/or sulfonylurea regimens.</p>	<p>as an HbA_{1c} 7.0 to 10.0%) with sulfonylurea and metformin therapy at maximally effective doses, enrolled in a previous 26 week study</p>		<p>Medical Outcomes Study 36-Item Short-Form Health Survey, Diabetes Treatment Flexibility Score</p> <p>Secondary: Not reported</p>	<p>measures).</p> <p>Neither the exenatide nor the insulin glargine group experienced a significant improvement in Treatment Flexibility Score scores (P=0.93 for both groups).</p> <p>Secondary: Not reported</p>
<p>Nauck et al.⁷⁶ (2007)</p> <p>Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs</p> <p>insulin aspart BID</p> <p>All patients were receiving existing metformin and/or sulfonylurea regimens.</p>	<p>MC, OL, RCT</p> <p>Patients 30 to 75 years of age who had suboptimal glycemic control despite receiving optimally effective metformin and sulfonylurea therapy for ≥3 months, HbA_{1c} levels ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m², and a history of stable body weight (≤10% variation for ≥3 months)</p>	<p>N=501</p> <p>52 weeks</p>	<p>Primary: Mean change in HbA_{1c} levels, weight, fasting serum glucose levels, PPG levels, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: There was not a significantly different change from baseline in mean HbA_{1c} levels between the exenatide (−1.04%) and insulin aspart groups (−0.89%, 95% CI, −0.32% to 0.01%; P=0.067).</p> <p>Patients in the exenatide group experienced a gradual weight loss of −2.5 kg, compared to a gradual weight gain of 2.9 kg in the insulin aspart group, (95% CI, −5.9 to −5.0; P<0.001) at the end of 52 weeks.</p> <p>Patients in both exenatide (−1.8 mmol/L) and insulin aspart (−1.7 mmol/L) groups had a significant decrease in fasting serum glucose compared to baseline (P<0.001 for both groups). There was not a significant difference between groups (CI, −0.6 to 0.4; P=0.689).</p> <p>Patients in the insulin aspart group had significantly lower mean glucose values at pre-breakfast (P=0.037), pre-lunch (P=0.004) and 03.00 hours (P=0.002). Patients in the exenatide group had a greater reduction in PPG excursions following morning (P<0.001), midday (P=0.002) and evening meals (P<0.001).</p> <p>The withdrawal rate was 21.3% in the exenatide group and 10.1% in the insulin aspart group. Adverse events that were more commonly reported in the exenatide vs insulin aspart group included: nausea (33.2 vs 0.4%), vomiting (15.0 vs 3.2%), diarrhea (9.5 vs 2%) and other clinically relevant adverse events (13.4 vs 6.4%).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Diamant et al.⁷⁷ (2010) DURATION-3</p> <p>Exenatide ER 2 mg SC once weekly</p> <p>vs</p> <p>insulin glargine SC QD</p> <p>All patients received existing background oral glucose-lowering regimens.</p>	<p>OL, PG, RCT</p> <p>Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m², and a stable body weight ≥3 months</p>	<p>N=456</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving HbA_{1c} <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell function, insulin profile, patient-reported QOL, safety</p>	<p>Not reported</p> <p>Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER (-1.5±0.05%) compared to insulin glargine (-1.3±0.06%; treatment difference, -0.16±0.07%; 95% CI, -0.29 to -0.03; P=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, HbA_{1c} was decreased by -1.5±0.06 and -1.4±0.07% (treatment difference, -1.8±0.08%; 95% CI, -0.34 to -0.02; P=0.031).</p> <p>Secondary: Significantly greater proportions of exenatide ER-treated patients achieved HbA_{1c} <7.0 (60 vs 48%; P=0.010) and <6.5% (35 vs 23%; P=0.004) compared to insulin glargine treated patients.</p> <p>Fasting serum glucose decreased with both treatments (-2.1±0.2 vs -2.8±0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; P=0.001).</p> <p>With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points (P<0.0001 for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour (P=0.022) and before breakfast (P<0.0001), and significantly lower concentrations with exenatide ER were observed after dinner (P=0.004). Exenatide ER resulted in significantly greater reductions in post-prandial glucose excursions compared to insulin glargine after morning (P=0.001) and evening meals (P=0.033).</p> <p>Seventy nine percent of patients receiving exenatide ER experienced both a decrease in HbA_{1c} and body weight compared to 63% of patients receiving insulin glargine who experienced a decrease in HbA_{1c} and increase in body weight.</p> <p>Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; P<0.05). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to 0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02)</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>observed.</p> <p>Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; $P<0.05$). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; $P<0.05$). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed.</p> <p>Both treatments resulted in improvements in IWQOL-Lite, binge eating scale, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported).</p> <p>Gastrointestinal events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. Gastrointestinal events were all mild or moderate and no serious adverse events were reported by more than one patient, except chest pain (two patients).</p>
<p>Diamant et al.⁷⁸ (2012) DURATION-3</p> <p>Exenatide ER 2 mg SC once weekly</p> <p>vs</p> <p>insulin glargine SC QD</p>	<p>ES of DURATION-3⁶⁰</p> <p>Type 2 diabetics ≥ 18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of $\geq 1,500$ mg for ≥ 8 months) or combined</p>	<p>N=390</p> <p>84 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportions of patients achieving HbA_{1c} < 7.0 and $\leq 6.5\%$, body weight, incidence of hypoglycemia, safety</p>	<p>Primary: At 84 weeks, HbA_{1c} decreased from baseline by -1.2% with exenatide ER compared to -1.0% with insulin glargine ($P=0.029$).</p> <p>Secondary: The proportions of patients who achieved end point HbA_{1c} targets < 7.0 and $\leq 6.5\%$ were 44.6 and 36.8% with exenatide ER and insulin glargine ($P=0.084$) and 31.3 and 20.2% with exenatide ER and insulin glargine ($P=0.009$), respectively.</p> <p>Patients receiving exenatide ER lost 2.1 kg of body weight compared to patients receiving insulin glargine who gained 2.4 kg ($P<0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received existing background oral glucose-lowering regimens.	metformin and sulfonylurea treatment ≥ 3 months, HbA _{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m ² , and a stable body weight ≥ 3 months			<p>Among patients receiving metformin plus a sulfonylurea, the incidence of minor hypoglycemia was 24 and 54% with exenatide ER and insulin glargine (P<0.001).</p> <p>Among adverse events occurring in $\geq 5\%$ of all patients, diarrhea (12 vs 6%) and nausea (15 vs 1%) occurred more frequently (P<0.05) with exenatide ER compared to insulin glargine.</p>
<p>Derosa et al.⁷⁹ (2011)</p> <p>Exenatide 5 μg SC BID, titrated up to 10 μg SC BID</p> <p>vs</p> <p>glimepiride 1 mg TID, titrated up to 2 mg TID</p>	<p>MC, RCT, SB</p> <p>Patients ≥ 18 years of age with type 2 diabetes intolerant to metformin at the highest dosages (2,500 to 3,000 mg/day)</p>	<p>N=111</p> <p>12 months</p>	<p>Primary: Change in baseline body weight, glycemic control, insulin resistance</p> <p>Secondary: Not reported</p>	<p>Primary: There was decrease of body weight and BMI after six, nine, and 12 months (P<0.05, P<0.01, P<0.001, respectively) with exenatide, not obtained with glimepiride. BMI reached with exenatide was significantly lower compared to glimepiride (P<0.05).</p> <p>A similar decrease in HbA_{1c}, FPG, and PPG after nine (P<0.05 for all), and after 12 months (P<0.01 for all) with both treatments, without significant differences between the two treatments.</p> <p>Exenatide resulted in a reduction of fasting plasma insulin, and HOMA-IR after 12 months (P<0.05 for both), not observed with glimepiride; fasting plasma insulin increased with glimepiride. Values reached with exenatide were significantly lower compared to values reached with glimepiride after 12 months (P<0.05).</p> <p>Exenatide, but not glimepiride, gave an increase of adiponectin after 12 months (P<0.05), and the value registered with exenatide was significantly higher compared to the value recorded with glimepiride at trial end (P<0.05).</p> <p>A decrease of tumor necrosis factor-α was observed after 12 months (P<0.05) with exenatide, but no with glimepiride; furthermore the value obtained with exenatide was significantly better compared to the value obtained with glimepiride after 12 months (P<0.05). Exenatide, but not glimepiride, gave a reduction of high sensitivity CRP after nine and 12 months (P<0.05 and P<0.01) compared to baseline and glimepiride (P<0.05).</p> <p>Secondary: Not reported</p>
Yang et al. ⁸⁰	AC, DB, DD, RCT	N=929	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2011)</p> <p>Liraglutide 0.6, 1.2, or 1.8 mg QD</p> <p>vs</p> <p>glimepiride 4 mg QD</p> <p>All patients received metformin.</p>	<p>Adult patients with type 2 diabetes</p>	<p>16 weeks</p>	<p>Change in baseline HbA_{1c}</p> <p>Secondary: Proportions of patients achieving HbA_{1c} <7.0 and ≤6.5%, body weight, BP, hypoglycemia, adverse events</p>	<p>Baseline HbA_{1c} was significantly reduced with all treatments. Treatment with liraglutide 1.2 and 1.8 mg was non-inferior to glimepiride (mean reduction: 1.36, 1.45, 1.39% points, respectively).</p> <p>Secondary: No significant difference was shown in the proportion of patients achieving HbA_{1c} <7.0 or ≤6.5% between liraglutide 1.2 and 1.8 mg and glimepiride.</p> <p>Liraglutide resulted in a mean reduction in weight of -1.8 to -2.4 kg compared to 0.1 kg weight gain with glimepiride.</p> <p>Liraglutide significantly reduced SBP compared to glimepiride.</p> <p>Two patients receiving glimepiride experienced major hypoglycemia compared to zero patients receiving liraglutide. Liraglutide was associated with a 10-fold lower incidence of minor hypoglycemia compared to glimepiride.</p> <p>Gastrointestinal disorders were the most commonly reported adverse events with liraglutide therapy; events were transient and resulted in few withdrawals.</p>
<p>Bergental et al.⁸¹ (2010) DURATION-2</p> <p>Exenatide ER 2 mg SC once weekly</p> <p>vs</p> <p>sitagliptin 100 mg QD</p> <p>vs</p> <p>pioglitazone 45 mg QD</p>	<p>DB, DD, MC, PG, RCT</p> <p>Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m²</p>	<p>N=514</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk</p>	<p>Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c} compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; P<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165).</p> <p>Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone.</p> <p>Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received existing metformin therapy.			markers, patient-reported QOL, safety	<p>FPG goal of ≤ 7 mmol/L compared to patients receiving sitagliptin (35%; $P < 0.0001$), but no difference was observed between patients receiving pioglitazone (52%; $P = 0.1024$).</p> <p>In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported).</p> <p>Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; $P = 0.0002$) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; $P < 0.0001$).</p> <p>Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0).</p> <p>Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 $\mu\text{IU/mL}$; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 $\mu\text{IU/mL}$ [95% CI, -1.6 to 2.3]; treatment difference, 3.2 $\mu\text{IU/mL}$ [95% CI, 0.6 to 5.8]; $P = 0.0161$) and pioglitazone (-3.9 $\mu\text{IU/mL}$ [95% CI, -5.9 to -2.0]; treatment difference, 7.5 $\mu\text{IU/mL}$ [95% CI, 4.9 to 10.1]; $P < 0.0001$).</p> <p>Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only).</p> <p>All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported).</p> <p>All five domains of weight-related QOL and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406).</p> <p>The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported.</p>
<p>Wyshman et al.⁸² (2011) DURATION-2</p> <p>Exenatide ER 2 mg SC once weekly (continued exenatide ER) vs exenatide ER 2 mg SC once weekly (switched to exenatide ER)</p> <p>Patients enrolled in DURATION-2 who were randomized to sitagliptin 100 mg QD or pioglitazone 45 mg QD were transitioned to exenatide ER 2 mg</p>	<p>ES (DURATION-2⁶⁴)</p> <p>Type 2 diabetics ≥18 years of age, receiving stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m²</p>	<p>N=319</p> <p>26 weeks (52 weeks total)</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, body weight, proportion of patients achieving an HbA_{1c} <7.0 or ≤6.5%, proportion of patients achieving FPG <7 mmol/L, and markers of cardiovascular risk at week 52 and from week 26 to 52; safety</p> <p>Secondary: Not reported</p>	<p>Primary: Patients who continued exenatide ER demonstrated significant 52 week improvements in HbA_{1c} (-1.6±0.1%), FPG (-1.8±0.3 mmol/L), and body weight (-1.8±0.5 kg; P=0.0002 vs baseline). Patients originally receiving sitagliptin who switched to exenatide ER demonstrated significant incremental improvements in HbA_{1c} (-0.3±0.1%; P=0.0010), FPG (-0.7±0.2 mmol/L; P=0.0017), and body weight (-1.1±0.3 kg; P=0.0006). Patients originally receiving pioglitazone who switched to exenatide ER maintained HbA_{1c} and FPG improvements (week 52, -1.6±0.1% and -1.7±0.3 mmol/L, with significant weight loss; -3.0±0.3 kg; P<0.0001).</p> <p>No differences in the proportions of patients achieving target HbA_{1c} <7.0 or ≤6.5% were observed between weeks 26 and 52 in patients who continued exenatide ER and who switched to exenatide ER from pioglitazone. A significantly greater proportion of patients achieved both targets after switching from sitagliptin to exenatide ER (P<0.05 for both). Similar results were observed for the FPG target (<7 mmol/L) (P=0.0002).</p> <p>Patients who continued exenatide ER achieved greater SBP improvements at week 52 (-12.2 mm Hg; 95% CI, -16.1 to -8.3). Patients with abnormal SBP at 26 weeks who were receiving sitagliptin and pioglitazone, achieved greater SBP decreases (-11.3 [95% CI, -14.9 to -7.7] and -9.4 mm Hg [95% CI, -13.4 to -5.3], respectively) at week 52. Patients who continued exenatide ER maintained improvements in HDL-C at week 52; all other lipid variables were not different from baseline. Patients switched to exenatide ER from</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SC once weekly after the initial 26 week trial period.				<p>sitagliptin maintained HDL-C improvements and achieved a significant decrease in TC at week 52. Patients switched to exenatide ER from pioglitazone achieved significant decreases in HDL-C, LDL-C, and TC at week 52. Patients who continued exenatide ER achieved improvements in urinary albumin/creatinine ratio, BNP, and high-sensitivity CRP. The urinary albumin/creatinine ratio was significantly decreased for all treatment groups by week 52. Patients who switched to exenatide ER from sitagliptin and pioglitazone achieved significant reductions in BNP, with high-sensitivity CRP and plasminogen activator inhibitor-1 improvements observed after 26 weeks of initial treatment with pioglitazone were not maintained once switched to exenatide ER.</p> <p>Exenatide ER was well tolerated and adverse events were predominantly mild or moderate in intensity. Nausea was the most frequent adverse event (continued exenatide ER, 5%; switched to exenatide ER from sitagliptin, 11%; switched to exenatide ER from pioglitazone, 10%). No major cases of hypoglycemia or pancreatitis were reported.</p> <p>Secondary: Not reported</p>
<p>Garber et al.⁸³ (2009) LEAD-3</p> <p>Liraglutide 1.2 and 1.8 mg SC QD</p> <p>vs</p> <p>glimepiride 8 mg/day</p>	<p>AC, DB, DD, MC, PG, RCT</p> <p>Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase</p>	<p>N=746</p> <p>52 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline body weight, FPG, eight-point self-measured glucose concentrations, BP, β cell function, fasting glucagon, and patient-reported QOL</p>	<p>Primary: Decreases in HbA_{1c} were $-0.84 \pm 1.23\%$ with liraglutide 1.2 mg, $-1.14 \pm 1.24\%$ with liraglutide 1.8 mg, and $-0.51 \pm 1.20\%$ with glimepiride. Decreases with liraglutide were significantly greater compared to glimepiride. Differences between glimepiride and liraglutide 1.2 mg were -0.62% (95% CI, -0.83 to -0.42; $P < 0.0001$) and liraglutide 1.8 mg were -0.33% (95% CI, -0.53 to -0.13; $P = 0.0014$). Additionally, decreases with liraglutide 1.8 mg were significantly greater compared to liraglutide 1.2 mg (-0.29%; 95% CI, -0.50 to -0.09; $P = 0.0046$).</p> <p>Secondary: Liraglutide-treated patients lost body weight and those receiving glimepiride gained weight (P values not reported). The weight loss with liraglutide after 16 weeks was sustained throughout the 52 weeks.</p> <p>Decreases in FPG with liraglutide (1.2 mg, -0.84 mmol/L; $P = 0.027$ and 1.8 mg, -1.42 mmol/L; $P = 0.0001$) were significantly greater compared to glimepiride (-0.29 mmol/L).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>inhibitors, and TZDs for ≥ 2 months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)</p>			<p>Decreases in PPG occurred with all three treatments (liraglutide 1.2 mg vs glimepiride; P=0.1616, liraglutide 1.8 mg vs glimepiride; P=0.0038, and liraglutide 1.8 mg vs liraglutide 1.2 mg; P=0.1319).</p> <p>Decreases in SBP were -0.7 mm Hg with glimepiride compared to -0.1 mm Hg with liraglutide 1.2 mg (P=0.2912) and -3.6 mm Hg with liraglutide 1.8 mg (P<0.0118). Mean DBP decreased but not significantly with any treatment.</p> <p>HOMA-IR and fasting glucagon significantly decreased with liraglutide, but increased with glimepiride. HOMA-IR was decreased by -0.65% with liraglutide 1.2 mg and by -1.35% with liraglutide 1.8 mg, and increased by 0.85% with glimepiride (P=0.0249 and P=0.0011 for liraglutide 1.2 and 1.8 mg vs glimepiride).</p> <p>Patients receiving liraglutide 1.8 mg reported improved QOL scoring for physical and emotional domains compared to glimepiride (P=0.02). Improvements were largely as a result of improvements in weight image and weight concern (P<0.01).</p>
<p>Garber et al.⁸⁴ (2011) LEAD-3 Liraglutide 1.2 mg and 1.8 mg SC QD vs glimepiride 8 mg/day</p>	<p>ES (LEAD-3⁶⁶) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and</p>	<p>N=440 52 weeks</p>	<p>Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, β cell function, fasting glucagon, and BP</p>	<p>Primary: The decrease in HbA_{1c} was significantly greater with liraglutide 1.2 mg (-0.9 vs -0.6%; P=0.0376) and 1.8 mg (-1.1 vs -0.6%; P=0.0016) compared to glimepiride over two years of treatment.</p> <p>Secondary: Over two years, patients receiving liraglutide 1.2 or 1.8 mg experienced weight loss compared to weight gain with patients receiving glimepiride (-2.3 and -2.8 vs 1.0 kg, respectively; P<0.001 for both comparisons).</p> <p>Compared to glimepiride (-1.8 mmol/L), both liraglutide 1.2 (-1.9 mmol/L) and 1.8 mg (-2.6 mmol/L) were significantly more effective at decreasing FPG over the course of the extension period (P=0.0015 and P=0.0001, respectively).</p> <p>In patients who completed two years of treatment, baseline HOMA-IR decreased by -1.1% with liraglutide 1.2 mg and -0.8% with liraglutide 1.8 mg, and increased by 0.8% with glimepiride (P=0.0451 for liraglutide</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	TZDs for ≥ 2 months; and HbA _{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)			<p>1.2 mg vs glimepiride).</p> <p>The proinsulin:insulin ratio increased slightly with all treatments, by 0.108 with liraglutide 1.2 mg, 0.018 with liraglutide 1.8 mg, and 0.141 with glimepiride (P values not reported).</p> <p>After two years, all three treatments had increases in HOMA-B, fasting insulin, and fasting C-peptide; and had decreases in fasting glucagon, but there were no differences between treatments (P values not reported).</p> <p>No differences between treatments in change in pulse, DBP, and SBP were observed in any patient completing two years of treatment.</p>
<p>Bode et al.⁸⁵ (2010) LEAD-3</p> <p>Liraglutide 1.2 and 1.8 mg SC QD</p> <p>vs</p> <p>glimepiride 8 mg/day</p>	<p>Post-hoc analysis (LEAD-3⁶⁶)</p> <p>Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥ 2 months and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering</p>	<p>N=746</p> <p>52 weeks</p>	<p>Primary: Impact of treatment on patient-reported perceptions of body image, weight, and weight concern; psychological well-being and distress, cognitive functioning and health</p> <p>Secondary: Not reported</p>	<p>Primary: Both measures of weight perception (weight assessment and weight concern) were more favorable with liraglutide compared to glimepiride. Baseline-adjusted mean weight assessment compared to the reference point “my weight is just right” was significantly more favorable (i.e., shifted from more overweight to less overweight) with liraglutide 1.8 mg (P=0.002). Furthermore, weight concern decreased markedly with liraglutide, with mean scores significantly less compared to glimepiride (liraglutide 1.2 mg; P<0.0001 and liraglutide 1.8 mg; P<0.001).</p> <p>Logistic regression estimates indicated that patients receiving liraglutide 1.8 mg were 52% less likely to report feeling either “somewhat” or “very overweight” vs “just right”, “somewhat underweight,” or “very overweight” during treatment compared to patients receiving glimepiride (OR, 0.480; 95% CI, 0.331 to 0.696; P value not reported). Also, liraglutide 1.8 mg-treated patients were 39% less likely to report being “somewhat worried”, “very worried,” or “extremely worried” vs “a little concerned” or “not concerned at all” about their weight during treatment compared to glimepiride treated patients (OR, 0.608; 95% CI, 0.440 to 0.850; P value not reported).</p> <p>There were no differences between liraglutide and glimepiride for the body image scales (body size evaluation and body appearance distress) or for any of the cognitive functioning and performance scales during treatment (P values not reported).</p> <p>The health-related QOL composite score significantly improved more</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	agent monotherapy)			<p>favorably with liraglutide 1.8 mg compared to glimepiride (P=0.004). Favorable improvements were seen in the composite scales of mental and emotional healthy, psychological well-being, psychological distress, and general perceived health (P<0.05 for all). The higher scores with liraglutide 1.8 mg for mental and emotional health reflected greater improvement in both domains of psychological well-being and psychological distress compared to glimepiride. There were no differences for these scales between liraglutide 1.2 mg and glimepiride (P values not reported). However, there was a significant difference between liraglutide 1.2 mg and glimepiride in general health status favoring liraglutide (P=0.006).</p> <p>Correlation analyses using data pooled from all treatments confirmed that decreases in BMI were correlated with improvements in both weight assessment and weight concern (P<0.0001 for both), indicating that patients' reports were valid representations of actual weight losses.</p> <p>Decreases in HbA_{1c} corresponded to improvements in general perceived health (P<0.0001), cognitive functioning composite score (P=0.006), and cognitive performance (P=0.004). Correlations of change in HbA_{1c} within treatment groups with change in patient-reported measures were strongest with liraglutide 1.8 mg.</p> <p>Secondary: Not reported</p>
<p>Charbonnel et al.⁸⁶ (2013)</p> <p>Sitagliptin starting at 100 mg/day, with glimepiride added if further glucose control needed (oral)</p> <p>vs</p> <p>liraglutide starting at 0.6 mg/day, up-</p>	<p>AC, OL, RCT</p> <p>Patients with type 2 diabetes mellitus aged 18 to 79 years, on a stable dose of metformin monotherapy $\geq 1,500$ mg/day for ≥ 12 weeks, with an HbA_{1c} $\geq 7.0\%$ and $\leq 11.0\%$ and a fasting fingerstick glucose < 15</p>	<p>N=653 (per protocol patients were analyzed, N=522)</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c} (non-inferiority)</p> <p>Secondary: FPG, plasma lipids, safety</p>	<p>Primary: HbA_{1c} decreased over 26 weeks in both treatment strategy groups, with a larger initial reduction at week 12 in the injectable strategy group. The mean change in HbA_{1c} at week 26 was -1.3% in the oral group and -1.4% in the injectable group. The primary hypothesis was met to declare that the oral treatment was non-inferior to the injectable in lowering HbA_{1c}.</p> <p>Secondary: Significant reductions in FPG at week 26 were observed in both groups, with a greater reduction observed in the injectable group. No meaningful between-group differences were found in any lipid variable or in the incidence of clinical adverse effects overall. The incidence of drug-related adverse events or adverse events leading to discontinuation was greater in the injectable group than in the oral group. These differences were mainly related to the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
titrated to 1.2 mg/day after 1 week (injectable)	mmol/L at the randomization visit, deemed capable by the investigator of using a Victoza pen injection device			significantly higher incidence of gastrointestinal adverse events, such as abdominal pain, diarrhea, nausea, and vomiting, in the injectable group.
Amori et al. ⁸⁷ (2007) Incretin therapy (exenatide, liraglutide, sitagliptin and vildagliptin*) vs non-incretin-based therapy (placebo or hypoglycemic agent)	MA (29 RCTs) Type 2 diabetics	N=12,996 Duration varied (12 to 52 weeks)	Primary: Change in baseline HbA _{1c} Secondary: FPG, proportion of patients achieving an HbA _{1c} <7.0%	Primary: Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA _{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81). Specifically, no difference in the HbA _{1c} was found in OL non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA _{1c} efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported). Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21). Exenatide-treated patients were more likely to achieve an HbA _{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in non-inferiority trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.
Pinelli et al. ⁸⁸ (2008) Exenatide in combination with other antidiabetic agents vs TZD in	MA (22 RCTs) Patients with type 2 diabetes receiving combination therapy	N=9,325 ≥24 weeks	Primary: Mean change in baseline HbA _{1c} Secondary: Proportion of patients reaching HbA _{1c} <7.0%, mean change from baseline in FPG	Primary: There were small reductions in HbA _{1c} across the trials. The WMD were -0.80% (95% CI, -1.10 to -0.50) with TZD and -0.60% (95% CI, -1.04 to -0.16) with exenatide. When only PC trials were analyzed, there were greater reductions in HbA _{1c} with both TZDs (WMD, -1.14%; 95% CI -1.30 to -0.98) and exenatide (WMD, -0.97%; 95% CI -1.11 to -0.83). When only TZD AC trials were analyzed, there was a significant difference in HbA _{1c} levels from baseline (WMD, -0.38%; 95% CI -0.75 to -0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination with other antidiabetic agents			and body weight, hypoglycemia, gastrointestinal adverse events	<p>There was no difference in HbA_{1c} reduction between exenatide and insulin comparators in OL, NI trials.</p> <p>Secondary: TZD and exenatide-based therapies were associated with OR of 2.27 (95% CI, 1.22 to 4.24) and 2.90 (95% CI, 1.28 to 6.55), respectively, for reaching HbA_{1c} <7.0%.</p> <p>FPG concentrations were reduced from baseline with TZD-based regimens (WMD, -29.58 mg/dL; 95% CI, -39.27 to -19.89), but did not reach significance with exenatide (WMD, -8.77 mg/dL; 95% CI, -28.85 to 11.31).</p> <p>Severe hypoglycemia was rare in the one exenatide and four TZD trials that identified a total of nine participants experiencing hypoglycemic episodes. In these five trials, participants reporting an event were also receiving an insulin secretagogue. The OR for developing nonsevere hypoglycemia with TZDs was not significantly different from other treatment arms (OR, 1.59; 95% CI, 0.76 to 3.32).</p> <p>In TZD trials, there was a nonsignificant difference in body weight from baseline compared to other treatment groups (WMD, 1.51 kg; 95% CI, -0.12 to 3.15). Mean change in body weight from baseline was reduced significantly with exenatide-based regimens (WMD, -2.74 kg; 95% CI, -4.85 to -0.64).</p> <p>The most commonly reported adverse effects were gastrointestinal disorders in the exenatide trials. ORs greater than one for nausea, vomiting, and diarrhea were observed with exenatide with pooled ORs of 9.02 (95% CI, 3.66 to 22.23), 4.56 (95% CI, 3.13 to 6.65), and 2.96 (95% CI, 2.05 to 4.26), respectively. Nausea occurred in 47% of patients receiving exenatide and 11% in the comparator arms. Vomiting occurred in 15% of patients receiving exenatide and 4% of patients receiving comparator. Diarrhea occurred in 12% of patients receiving exenatide and 4% in patients receiving comparator.</p>

*Agent is not available in the United States.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, XL=extended-release

Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-dummy, ES=extension study, IA=interim analysis, MC=multicenter, NI=noninferiority, OE=open-ended, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, RETRO=retrospective, SB=single-blind, SR=systematic review, TB=triple-blind, XO=cross-over

Miscellaneous abbreviations: ALT=alanine aminotransferase, apo B=apolipoprotein B, AST=aspartate aminotransferase, AUC=area under the curve, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, CI=confidence interval, COPD=chronic obstructive pulmonary disease, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, LSM=least squares mean, MI=myocardial infarction, PAI-1=plasminogen activator inhibitor-1, OR=odds ratio, PPG=post-prandial glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TZD=thiazolidinedione, VLDL-C=very low density lipoprotein cholesterol, WMD=weighted mean difference

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 12. Relative Cost of the Incretin Mimetics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Albiglutide	injection	Tanzeum®	\$\$\$\$\$	N/A
Dulaglutide	injection	Trulicity®	\$\$\$\$\$	N/A
Exenatide	injection	Byetta®, Bydureon®	\$\$\$\$\$	N/A
Liraglutide	injection	Victoza®	\$\$\$\$\$	N/A

N/A=Not available

X. Conclusions

The incretin mimetics are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.⁷ Albiglutide, dulaglutide, exenatide, and liraglutide are included in this review. There are no generic products in this class.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The incretin mimetics are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, an established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the

potential for weight loss as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents. Patients who are not appropriate for initial therapy with metformin may be initiated on another oral antidiabetic agent, such as an SGLT2 inhibitor, sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one incretin mimetic over another is not stated.⁸⁻²⁰

A variety of clinical trials have been conducted evaluating the incretin mimetics. The incretin mimetics have been evaluated in combination with and in comparison to a variety of antidiabetic therapies. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens. Overall, the incretin mimetics are effective in improving glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, post-prandial glucose, and body weight. Efficacy data comparing the incretin mimetics to other antidiabetic agents are not consistent, with the incretin mimetics achieving significantly greater or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents. A limited number of head-to-head clinical trials have been conducted within the class. Results from these trials do not consistently demonstrate that one incretin mimetic is more effective than another.²²⁻⁸⁸ The newest agent, dulaglutide, has been demonstrated to be non-inferior to liraglutide therapy in two clinical trials.^{23,41}

Gastrointestinal-related adverse events are common with incretin mimetics.¹⁻⁷ There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking these agents.¹⁻⁵ There have also been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis or kidney transplantation.¹⁻⁵ Patients may develop antibodies to the incretin mimetics consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals.¹⁻⁵

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the incretin mimetics.¹⁻⁵

There is insufficient evidence to support that one brand incretin mimetic is safer or more efficacious than another within its given indication. Since the incretin mimetics are not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, they should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand incretin mimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Byetta[®] [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals LP; 2015 Feb.
2. Bydureon[®] [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals LP.; 2015 Sep.
3. Victoza[®] [package insert]. Plainsboro (NJ): Novo Nordisk Inc.; 2016 Apr.
4. Tanzeum[™] [package insert]. Wilmington (DE): GlaxoSmithKline, LLC; 2016 Sep.
5. Trulicity[®] [package insert]. Indianapolis (IN): Eli Lilly and Company; 2017 Jan.
6. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Feb]. Available from: <http://www.thomsonhc.com/>.
7. Facts and Comparisons[®] eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Feb 2017]. Available from: <http://online.factsandcomparisons.com>.
8. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2016;39(Suppl. 1):S1–S112.
9. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.
10. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015 Mar;58(3):429-42.
11. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.
12. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1:1-87.
13. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. Endocr Pract. 2016;22(1):84-113.
14. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
15. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
16. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
17. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131(2):364-382.
18. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.
19. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.
20. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care 2014;37(7):2034-2054.
21. Bischoff LA, Jabbour SA, Miller JL. Exenatide once weekly in type 2 diabetes mellitus. Expert Opin Pharmacother. 2011;128(8):1927-303.
22. Nauck MA, Stewart MW, Perkins C, et al. Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 2): 52 week primary endpoint results from a randomised, placebo-controlled trial in patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetologia. 2016 Feb;59(2):266-74.

23. Miyagawa J, Odawara M, Takamura T, et al. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. *Diabetes Obes Metab.* 2015 Oct;17(10):974-83.
24. Moretto TJ, Milton DR, Ridge TD, Macconell LA, Okerson T, Wolka AM, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther.* 2008;30(8):1448-60.
25. DeFronzo RA, Okerson T, Viswanathan P, et al. Effects of exenatide versus sitagliptin on postprandial glucose, insulin, and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. *Curr Med Res Opin.* 2008;24(10): 2943-52.
26. Bergenstal R, Lewin A, Bailey T et al. Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. *Curr Med Res Opin.* 2009;25(1): 65-75.
27. Xu W, Bi Y, Sun Z, et al. Comparison of the effects on glycaemic control and β -cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE study). *J Intern Med.* 2015 Jan;277(1):137-50.
28. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzolez JG, Chan M, et al. Efficacy and safety of exenatide once weekly vs metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4). *Diabetes Care.* 2012;35:252-8.
29. Fakhoury WKH, LeReun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. *Pharmacology.* 2010;86(1):44-57.
30. Monami M, Cremasco F, Lamanna C, Colombi C, Desideri CM, Iacomelli I, et al. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. *Exp Diabetes Res.* 2011;2011:215764.
31. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD006423. DOI: 10.1002/14651858.CD006423.pub2.
32. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared to exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. *Ann Pharmacother.* 2011;45:850-60.
33. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract.* 2008 Feb;79(2):196-203.
34. Pratley RE, Nauck MA, Barnett AH, Feinglos MN, Ovalle F, Harman-Boehm I, et al. Once weekly albiglutide vs once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomized, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol.* 2014;2(4):289-97
35. Reusch J, Stewart MW, Perkins CM, et al. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. *Diabetes Obes Metab.* 2014 Dec;16(12):1257-64.
36. Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia.* 2014 Dec;57(12):2475-84.
37. Home PD, Shamanna P, Stewart M, et al. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. *Diabetes Obes Metab.* 2015 Feb;17(2):179-87.
38. Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. *Diabetes Care.* 2014 Oct;37(10):2723-30.
39. Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2). *Diabetes Care.* 2015 Dec;38(12):2241-9.
40. Blonde L, Jendle J, Gross J, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet.* 2015 May 23;385(9982):2057-66.

41. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014 Oct 11;384(9951):1349-57.
42. Dungan KM, Weitgasser R, Perez Manghi F, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). *Diabetes Obes Metab*. 2016 May;18(5):475-82.
43. Weinstock RS, Guerci B, Umpierrez G, Nauck MA, Skrivaneck Z, Milicevic Z. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. *Diabetes Obes Metab*. 2015 Sep;17(9):849-58.
44. Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AY, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med*. 2011 Jan 18;154(2):103-12.
45. Rosenstock J, Shenouda SK, Bergenstal RM, Buse JB, Glass LC, Heilmann CR, et al. Baseline factors associated with glycemic control and weight loss when exenatide twice daily is added to optimized insulin glargine in patients with type 2 diabetes. *Diabetes Care*. 2012;35:955-8.
46. Okerson T, Yan P, Stonehouse A, Brodows R. Effects of exenatide on systolic blood pressure in subjects with type 2 diabetes. *Am J Hypertens*. 2010;23:334-9.
47. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* 2012;381(9861):117-124.
48. Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet* 2012; 379(9833):2270-2278.
49. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD, Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care*. 2004 Nov;27(11):2628-35.
50. DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2005 May;28(5):1092-100.
51. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care*. 2005 May;28(5):1083-91.
52. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes Metab*. 2015 Mar;17(3):268-75.
53. Scherthaner G, Rosas-Guzmán J, Dotta F, et al. Treatment escalation options for patients with type 2 diabetes after failure of exenatide twice daily or glimepiride added to metformin: results from the prospective European Exenatide (EUREXA) study. *Diabetes Obes Metab*. 2015 Jul;17(7):689-98.
54. Zinman B, Hoogwerf BJ, Garcia SD, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes. *Ann Intern Med*. 2007;146:477-85.
55. Ratner RE, Maggs D, Nielson LL, et al. Long-term effects of exenatide therapy over 82 weeks on glycemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2006 Jul;8(4):419-28.
56. Riddle MC, Henry RR, Poon TH, et al. Exenatide elicits sustained glycemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulfonylureas with or without metformin. *Diabetes Metab Res Rev*. 2006 Nov-Dec;22:483-91.
57. Blonde L, Klein EJ, Zhang B, et al. Interim analysis of the effects of exenatide treatment on A1C, weight, and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab*. 2006 Jul;8(4):436-47.
58. Buse JB, Klonoff DC, Nielsen LL, et al. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. *Clin Ther*. 2007;29(1):139-53.
59. Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008 Jan;24(1):275-86.
60. Viswanathan P, Chaudhuri A, Bhatia R, et al. Exenatide therapy in obese patients with type 2 diabetes mellitus treated with insulin. *Endocr Pract*. 2007;13:444-50.

61. Grimm M, Han J, Weaver C, et al. Efficacy, safety, and tolerability of exenatide once weekly in patients with type 2 diabetes mellitus: an integrated analysis of the DURATION trials. *Postgrad Med* 2013;125(3):47-57.
62. Marre M, Shaw J, Brandle M, Bebakar WMW, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared to adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med*. 2009;26:268-78.
63. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IS, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. *Diabetes Care*. 2009;32:84-90.
64. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care*. 2009 Jul;32(7):1224-30.
65. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016 Jul 28;375(4):311-22.
66. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulphonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomized controlled trial. *Diabetologia*. 2009;52:2046-55.
67. Kaku K, Rasmussen MF, Clauson P, Seino Y. Improved glycaemic control with minimal hypoglycemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 patients. *Diabetes Obes Metab*. 2010;12:341-7.
68. Ahmann A, Rodbard HW, Rosenstock J, et al. Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2015 Nov;17(11):1056-64.
69. Drucker D, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, et al. Exenatide once weekly vs twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study. *Lancet*. 2008;372:1240-50.
70. Buse JB, Drucker DJ, Taylor KL, Kim T, Walsh B, Hu H, et al. DURATION-1: exenatide once weekly produces sustained glycaemic control and weight loss over 52 weeks. *Diabetes Care*. 2010;33:1255-61.
71. Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycaemic control compared to exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96:1301-10.
72. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374(9683):39-47.
73. Buse JB, Sesti G, Schmidt WE, Montanya E, Chang CT, Xu Y, et al. Switching to once-daily liraglutide from twice-daily exenatide further improves glycaemic control in patients with type 2 diabetes using oral agents. *Diabetes Care*. 2010;33:1,300-3.
74. Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. 2005;143(8):559-69.
75. Secnik Boye K, Matza LS, Oglesby A, et al. Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes. *Health Qual Life Outcomes*. 2006;4:80.
76. Nauck MA, Duran S, Kim D. et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulphonylurea and metformin: a non-inferiority study. *Diabetologia*. 2007;50(2):259-67.
77. Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, et al. Once weekly exenatide compared to insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomized trial. *Lancet*. 2010;375:2234-43.
78. Diamant M, Van Gaal L, Stranks S, Guerci B, MacConell L, Haber H, et al. Safety and efficacy of once-weekly exenatide compared to insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. *Diabetes Care*. 2012;35:683-9.
79. Derosa G, Putignano P, Bossi A, Bonaventura A, Querci F, Franzetti IG, et al. Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type diabetic patients. *European Journal of Pharmacology*. 2011;666:251-6.
80. Yang W, Chen L, Ji Q, Liu X, Ma J, Tandon N, et al. Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial. *Diabetes, Obesity and Metabolism*. 2011;13:81-8.

81. Bergenstal RM, Wysham C, MacConell L, Malloy J, Walsh B, Yan P, et al. Efficacy and safety of exenatide once weekly vs sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomized trial. *Lancet*. 2010;376:431-9.
82. Wysham C, Bergenstal R, Malloy J, Yan P, Walsh B, Malone J, et al. DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide. *Diabet Met*. 2011;28:705-14.
83. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, et al. Liraglutide vs glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-weeks, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373:473-81.
84. Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycemic control and weight for two years as monotherapy compared to glimepiride in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011 Apr;13(4):348-56.
85. Bode BW, Testa MA, Magwire M, Hale PM, Hammer M, Blonde L, et al. Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. *Diabetes Obes Metab*. 2010;12:604-12.
86. Charbonnel B, Steinberg H, Eymard E, et al. Efficacy and safety over 26 weeks of an oral treatment strategy including sitagliptin compared with an injectable treatment strategy with liraglutide in patients with type 2 diabetes mellitus inadequately controlled on metformin: a randomised clinical trial. *Diabetologia* 2013; 56:1503–1511.
87. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA*. 2007;298(2):194-206.
88. Pinelli NR, Cha R, Brown MB, Jaber LA. Addition of thiazolidinedione or exenatide to oral agents in type 2 diabetes: a meta-analysis. *Ann Pharmacother*. 2008;42(11):1541-51.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Insulins
AHFS Class 682008
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Insulins stimulate peripheral glucose uptake by skeletal muscle and fat, decrease hepatic glucose production, inhibit lipolysis and proteolysis, and enhance protein synthesis.¹⁻²⁰ There are two types of insulin preparations currently available: human insulin and insulin analogs. Human insulin is derived from a biosynthetic process and is structurally identical to endogenous insulin. Insulin analogs are structurally different than human insulin. Each insulin analog differs in the addition, deletion, or substitution of amino acids on the B chain. These modifications lead to a faster onset and shorter duration of action (for rapid-acting insulin analogs) or slower absorption and a longer duration of action (for long-acting insulin analogs) than human insulins.^{1,2}

The insulin preparations are further categorized based on their duration of action. Rapid- and short-acting insulins are administered as a bolus prior to meals to control postprandial glucose excursions. They may also be administered continuously via an infusion pump. Intermediate- and long-acting insulins are administered once or twice daily. They act as basal insulin to decrease hepatic glucose production and lower fasting plasma glucose concentrations.^{1,2}

Three agents have been FDA-approved since the last review. Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection.^{1,2} Regular insulin is also formulated as an inhalation.¹⁸ Inhaled insulin powder is formulated in disposable, single-use cartridges, known as Technosphere[®], which provide a more efficient inhalation device than what has been used in the past.¹⁸ Regular insulin as used in Afrezza[®] is rapid-acting. Following pulmonary absorption into systemic circulation, the metabolism and elimination are comparable to regular human insulin.¹⁸ Tresiba[®] (insulin degludec) is a long-acting human insulin analog which forms multi-hexamers when injected into the subcutaneous tissue resulting in a depot. The protracted time action profile (>42 hours) is predominantly due to delayed absorption into the systemic circulation and to a lesser extent due to binding to circulating albumin.^{1,19} All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Two agents are also formulated with a higher concentration, regular insulin as 500 units/mL (U-500; Humulin[®] R U-500) and insulin glargine as 300 units/mL (U-300; Toujeo[®]).^{1,2} Toujeo[®] shows a more flat-line pharmacokinetic profile and prolonged duration of activity versus insulin glargine U-100 (Lantus[®]).²⁰

The insulins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic formulations of insulin; however, there are several products available over-the-counter. This class was last reviewed in February 2015.

Table 1. Insulins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Rapid-Acting Insulins			
Insulin aspart	injection	NovoLog [®]	NovoLog [®]
Insulin glulisine	injection	Apidra [®] , Apidra Solostar [®]	none
Insulin lispro	injection	Humalog [®]	none
Short-Acting Insulins			

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Insulin regular, human	inhalation, injection	Afrezza [®] , Humulin [®] R, Novolin [®] R	Humulin [®] R, Novolin [®] R
Intermediate-Acting Insulins			
NPH, human insulin isophane	injection	Humulin [®] N, Novolin [®] N	Humulin [®] N, Novolin [®] N
Long-Acting Insulins			
Insulin degludec	injection	Tresiba [®]	none
Insulin detemir	injection	Levemir [®]	Levemir [®]
Insulin glargine, human recombinant analog	injection	Lantus [®] , Lantus Solostar [®] , Toujeo [®]	Lantus [®]
Combination Insulins (Intermediate-Acting and Rapid-Acting)			
Insulin aspart protamine and insulin aspart	injection	NovoLog [®] Mix 70/30	NovoLog [®] Mix 70/30
Insulin lispro protamine and insulin lispro	injection	Humalog [®] Mix 50/50, Humalog [®] Mix 75/25	none
Combination Insulins (Intermediate-Acting and Short-Acting)			
NPH, human insulin isophane and insulin regular, human	injection	Humulin [®] 70/30, Novolin [®] 70/30	Humulin [®] 70/30, Novolin [®] 70/30

†Product is available over-the-counter.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Insulins

Clinical Guideline	Recommendation(s)
American Diabetes Association: Standards of Medical Care in Diabetes (2016) ²¹	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <p>Prevention or delay of type 2 diabetes</p> <ul style="list-style-type: none"> An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus. Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p>Glycemic goals in adults</p> <ul style="list-style-type: none"> Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include

Clinical Guideline	Recommendation(s)
	<p>those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.</p> <ul style="list-style-type: none"> • Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p><u>Pharmacologic therapy for type 1 diabetes</u></p> <ul style="list-style-type: none"> • Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. • Most patients should use of insulin analogs to reduce hypoglycemia risk. • Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. <p><u>Pharmacologic therapy for type 2 diabetes</u></p> <ul style="list-style-type: none"> • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If the A_{1c} target is not achieved after approximately three months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • Pregestational Diabetes <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1c} <6.5%, to reduce the risk of congenital anomalies. ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. • Gestational Diabetes Mellitus <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and

Clinical Guideline	Recommendation(s)
	<p>metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data.</p> <ul style="list-style-type: none"> • General Principles for Management of Diabetes in Pregnancy <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. • Due to increased red blood cell turnover, A_{1C} is lower in normal pregnancy than in normal nonpregnant women. The A_{1C} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012 and 2015 Update)^{22,23}</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects,

Clinical Guideline	Recommendation(s)						
	<p>potential for weight gain, and hypoglycemia should play a major role in drug selection.</p> <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> • Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. • Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. • In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. • Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. 						
	Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations						
	Initial Drug Monotherapy		Metformin				
	Efficacy (↓HbA _{1c})		High				
	Hypoglycemia		Low risk				
	Weight		Neutral/loss				
	Side Effects		Gastrointestinal/lactic acidosis				
	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)						
	Two Drug Combinations	Metformin + sulfonyl-urea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)
	Efficacy (↓HbA _{1c})	High	High	Inter-mediate	Inter-mediate	High	Highest
	Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk
	Weight	Gain	Gain	Neutral	Loss	Loss	Gain
	Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia
	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)						
	Three	Metformin	Metformin	Metformin	Metformin	Metformin	Metformin

Clinical Guideline	Recommendation(s)						
	Drug Combinations + sulfonyl-urea +	+ TZD +	+ DPP-4 inhibitor +	+ SGLT2 inhibitor +	+ GLP-1 receptor agonist +	+ insulin therapy +	
	TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin	Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin	Sulfonyl-urea, TZD, or insulin	TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist	
	If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents						
	More Complex Insulin Strategies	Combination injectable therapy					
American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012) ²⁴	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. 						
American Association of Clinical Endocrinologists/ American College Of Endocrinology: Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015) ²⁵	Antihyperglycemic pharmacotherapy for type 2 diabetes <ul style="list-style-type: none"> The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement. Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because 						

Clinical Guideline	Recommendation(s)
	<p>they have a more rapid onset and offset of action and are associated with less hypoglycemia.</p> <ul style="list-style-type: none"> • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists: Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm 2016 (2016)²⁶</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • The therapeutic regimen should be as simple as possible to optimize adherence. <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ Sodium glucose cotransporter 2 (SGLT-2) inhibitors. ○ DPP-4 inhibitors. ○ . ○ TZDs (use with caution). ○ Alpha-glucosidase inhibitors. • sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target

Clinical Guideline	Recommendation(s)
	<p>HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin.</p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ DPP-4 inhibitors. ○ TZD. ○ Basal insulin. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Three-drug combination therapy</u></p> <ul style="list-style-type: none"> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Insulin therapy algorithm</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the

Clinical Guideline	Recommendation(s)
	<p>recommended target by the addition of further oral antidiabetic drugs.</p> <p><u>Basal insulin</u></p> <ul style="list-style-type: none"> • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glyceic goals. • Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p><u>Basal-bolus insulin regimens</u></p> <ul style="list-style-type: none"> • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glyceic goals. <p><u>Basal insulin and incretin therapy regimens</u></p> <ul style="list-style-type: none"> • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last updated July 2016)²⁷</p>	<p><u>Individualized care</u></p> <ul style="list-style-type: none"> • Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective. • Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p><u>HbA_{1c} targets</u></p> <ul style="list-style-type: none"> • Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. • For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. • In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> ○ reinforce advice about diet, lifestyle and adherence to drug treatment and

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ support the person to aim for an HbA_{1c} level of 7.0% and ○ intensify drug treatment. ● Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> ○ who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy ○ for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job ○ for whom intensive management would not be appropriate, for example, people with significant comorbidities. ● If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p>Drug treatment</p> <ul style="list-style-type: none"> ● For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost ● If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. ● Initial drug treatment <ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m²: <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p>First intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. • Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes. <p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment. • If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. • Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in six months). • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment. • In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p>Insulin-based treatments</p> <ul style="list-style-type: none"> • When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional. ● When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. ● Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation. ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: <ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals. ○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes: <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. ● Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). ● Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. ● Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
Institute for Clinical Systems Improvement:	<ul style="list-style-type: none"> ● Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8%

Clinical Guideline	Recommendation(s)
<p>Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)²⁸</p>	<p>may be more appropriate when:</p> <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. <ul style="list-style-type: none"> ● A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. ● Recommend education and self-management, as appropriate. ● Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. ● Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes (2012)²⁹</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> ● Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. ● Match the timing of medication (including insulin) and meals. ● Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. ● Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals. ● Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. ● Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> ● Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. ● A lower HbA_{1c} target may be considered if it is easily and safely achieved. ● A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> ● Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. ● Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. • Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. • Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering mediations (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and</p>	<ul style="list-style-type: none"> • Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations ≥ 250 mg/dL. ○ Whose HbA_{1c} is >9%.

Clinical Guideline	Recommendation(s)
<p>Adolescents (2013)³⁰</p>	<ul style="list-style-type: none"> • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
<p>National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November 2016)³¹</p>	<p>Education and information for children and young people with type 1 diabetes</p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. • Tailor the education programme to each child or young person with type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. • Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Encourage children and young people with type 1 diabetes to wear or carry

Clinical Guideline	Recommendation(s)
	<p>something that identifies them as having type 1 diabetes (e.g., a bracelet).</p> <ul style="list-style-type: none"> • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. • Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations. • Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p><u>Insulin therapy for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. • Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen. • Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. • Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. • Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. • Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin

Clinical Guideline	Recommendation(s)
	<p>infusion users.</p> <ul style="list-style-type: none"> • Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. • Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin (0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%. • Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. • Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. • Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with type 1 diabetes a review of injection sites at each clinic visit. • Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. • If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily injections, continuous subcutaneous insulin infusion [CSII or insulin pump] therapy or once-, twice- or three-times daily mixed insulin injections). <p><u>Oral medicines for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. <p><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. • Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. • Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. • Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain.

Clinical Guideline	Recommendation(s)
	<p>Education and information for children and young people with type 2 diabetes</p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ HbA_{1c} monitoring and targets ○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control ○ the aims of metformin therapy and possible adverse effects ○ the complications of type 2 diabetes and how to prevent them. • Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every 2 years. • Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. <p>Dietary management for children and young people with type 2 diabetes</p> <ul style="list-style-type: none"> • At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. • Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. • At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. • Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. • Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. • At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI. • Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. • Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy. <p><u>Metformin</u></p> <ul style="list-style-type: none"> • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management (Published 2015; last updated July 2016)³²</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> • Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. • Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target. • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles ○ total glycated hemoglobin estimation (if abnormal hemoglobins). • Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. • Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia. • Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p><u>Self-monitoring of blood glucose</u></p> <ul style="list-style-type: none"> • Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least four times a day, including before each meal and before bed. • Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). • Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. • Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy) • Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking. <p><u>Continuous glucose monitoring</u></p> <ul style="list-style-type: none"> • Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. • Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause. ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level ≥9%) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in HbA_{1c} of 2.5% or more. • For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. <p><u>Insulin regimens</u></p> <ul style="list-style-type: none"> • Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. • Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only). <p><u>Long-acting insulin</u></p> <ul style="list-style-type: none"> • Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. • Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul style="list-style-type: none"> ○ an existing insulin regimen being used by the person that is achieving their agreed targets ○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. • Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p><u>Rapid-acting insulin</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. • Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. • If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. <p><u>Mixed insulin</u></p> <ul style="list-style-type: none"> • Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal-bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. • Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p><u>Optimizing insulin therapy</u></p> <ul style="list-style-type: none"> • For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously optimized insulin regimen, the following should be considered: <ul style="list-style-type: none"> ○ injection technique ○ injection sites ○ self-monitoring skills ○ knowledge and self-management skills ○ nature of lifestyle ○ psychological and psychosocial difficulties ○ possible organic causes such as gastroparesis. • Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. <p><u>Adjuncts</u></p> <ul style="list-style-type: none"> • Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> • Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. • Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. • Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. • After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. • Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. • Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. • Check injection site condition at least annually and if new problems with blood glucose control occur.

Clinical Guideline	Recommendation(s)
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)³³</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> • Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. • If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <p><u>Glycemic control goals</u></p> <ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood

Clinical Guideline	Recommendation(s)
	<p>glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise.</p> <ul style="list-style-type: none">• Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p> <ul style="list-style-type: none">• Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals.• Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required.• Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the insulins are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Insulins³⁻²⁰

Indication	Rapid-Acting Insulins			Short-Acting Insulins	Intermediate-Acting Insulins
	Insulin Aspart	Insulin Glulisine	Insulin Lispro	Insulin Regular, Human	NPH, Human Insulin Isophane
Adjunct to diet and exercise to improve glycemic control in adults and children with diabetes				✓ (Humulin® R)	
Improve glycemic control in adult patients with diabetes mellitus.				✓*	
Improve glycemic control in adults and children with diabetes mellitus	✓	✓	✓	✓ (Novolin® R)	✓
Treatment of diabetic patients with marked insulin resistance (daily requirements more than 200 units), since a large dose may be administered subcutaneously in a reasonable volume				✓ †	

* Afrezza®. Regular insulin as used in Afrezza® is rapid-acting.

† Humulin® R (U 500)

Table 4. FDA-Approved Indications for the Insulins (Continued)³⁻²⁰

Indication	Long-Acting Insulins			Combination Insulins (Intermediate-Acting and Rapid-Acting)		Combination Insulins (Intermediate-Acting and Short-Acting)
	Insulin Detemir	Insulin Degludec	Insulin Glargine, Human Recombinant Analog	Insulin Aspart Protamine/ Insulin Aspart	Insulin Lispro Protamine/ Insulin Lispro	NPH, Human Insulin Isophane/ Insulin Regular, Human
Improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus			✓ (Lantus®)			
Improve glycemic control in adult patients with diabetes mellitus			✓ (Toujeo®)	✓		✓
Improve glycemic control in adults and children with diabetes mellitus	✓	✓				
Treatment of patients with diabetes for the control of hyperglycemia					✓	

IV. Pharmacokinetics

The pharmacokinetic parameters of the insulins are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Insulins^{1,2}

Generic Name(s)	Onset (hours)	Peak (hours)	Duration (hours)	Half-Life (hours)	Mixing of Insulins
Rapid-Acting Insulins					
Insulin aspart	0.25	1 to 3	3 to 5	1.35	NPH
Insulin glulisine	0.2 to 0.5	Not reported	5.3	0.7	NPH
Insulin lispro	Not reported	0.5 to 1.5	3 to 4	0.43 to 0.87	May be mixed with longer-acting insulin
Short-Acting Insulins					
Insulin regular, human	0.5 to 2.5	2 to 15	8 to 22	1.4 to 3.3	May be mixed with longer-acting insulin
Intermediate-Acting Insulins					
NPH, human insulin isophane	0.5 to 1.5	2 to 12	24	Not reported	Insulin regular, human
Long-Acting Insulins					
Insulin degludec	1	9	Not reported	25	Insulin aspart
Insulin detemir	3 to 4	6 to 8	5.7 to 23.2	5 to 7	None
Insulin glargine, human recombinant analog	1.1	5	10.8 to 24	Not reported	None
Combination Insulins (Intermediate-Acting and Rapid-Acting)					
Insulin aspart protamine and insulin aspart	Not reported	Not reported	Not reported	Not reported	None
Insulin lispro protamine and insulin lispro	Not reported	Not reported	Not reported	Not reported	None
Combination Insulins (Intermediate-Acting and Short-Acting)					
NPH, human insulin isophane and insulin regular, human	Not reported	Not reported	Not reported	Not reported	None

Inh=inhaled human insulin

V. Drug Interactions

Major drug interactions with the insulins are listed in Table 6.

Table 6. Major Drug Interactions with the Insulins¹

Generic Name(s)	Interaction	Mechanism
Insulin	β -Adrenergic blocking agents (β -blockers), nonselective	β -blockers may blunt the sympathetic mediated response to hypoglycemia and may mask hypoglycemic symptoms. Discontinue nonselective β -blocker therapy or switch to a β -blocker with selective activity if possible.
Insulin	Metreleptin	Concurrent use of metreleptin and insulin may result in increased risk of hypoglycemia.
Insulin	Monoamine oxidase inhibitors (MAOIs)	MAOIs may potentiate the hypoglycemic effects of insulin by stimulating insulin secretion and inhibiting gluconeogenesis. Monitor blood glucose concentrations and adjust the dose of insulin as needed.
Insulin	Salicylates	Salicylates increase basal insulin secretion and acute insulin response to a glucose load. The hypoglycemic effects of insulin

Generic Name(s)	Interaction	Mechanism
		may be potentiated. Monitor blood glucose concentrations and adjust the dose of insulin as needed.

VI. Adverse Drug Events

Adverse events with the insulin products are rare and are similar among the various products.¹⁻²⁰

Hypoglycemia is the most common adverse event reported with insulin therapy. Because of the differences in onset and duration of action, the timing of hypoglycemia can vary between insulin formulations. Hypoglycemia risk may be increased when patients receive excessive doses of insulin, reduce their caloric intake, increase physical activity, during illnesses, or when receiving medications that increase the hypoglycemic effects of insulin.¹⁻²⁰

Redness, swelling, and itching at the injection site may result if administration is not done properly, if the skin is sensitive to cleansing solution, or if the patient is allergic to insulin or components of the insulin formulation.¹⁻²⁰

Generalized insulin allergies are rare but may present as a skin rash over the body, shortness of breath, fast pulse, sweating, a drop in blood pressure, bronchospasm, shock, anaphylaxis, or angioedema.¹⁻²⁰

A range of different chest symptoms were reported as adverse events associated with insulin therapy and were grouped under a nonspecific term chest pain.¹⁻²⁰

The Afrezza® labeling includes a boxed warning for the risk of acute bronchospasm in patients with chronic lung disease, with the following warnings¹⁸:

- Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza®.
- Afrezza® is contraindicated in patients with chronic lung disease such as asthma or COPD.
- Before initiating Afrezza®, perform a detailed medical history, physical examination, and spirometry (FEV₁) to identify potential lung disease in all patients.

VII. Dosing and Administration

The usual dosing regimens for the insulins are listed in Table 7. The dose of insulin is dependent upon the patient's glycemic response to food intake and exercise. Dose frequency and timing is dependent upon blood glucose levels, food consumption, time and level of exercise, as well as the insulin formulation used. Thus, an insulin regimen must be individualized to suit the specific needs and treatment goals of the patient.

Table 7. Usual Dosing Regimens for the Insulins¹⁻²⁰

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Rapid-Acting Insulins			
Insulin aspart	<p><u>Diabetes:</u> Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously.</p> <p>SC injection: inject immediately (within 5 to 10 minutes) before a meal</p> <p>CSII: approximately 50% of the total dose is usually given as meal-related boluses and the remainder is given as a basal infusion. Pre-meal boluses of</p>	<p>Insulin aspart has not been studied in pediatric patients younger than 2 years of age or in pediatric patients with type 2 diabetes.</p> <p><u>Type 1 diabetes:</u> Dosage must be individualized. May be administered via SC injection and as CSII by external pump.</p> <p>SC injection: inject immediately (within 5 to 10 minutes) before a meal</p>	<p>Cartridge: 100 U/mL</p> <p>Pen: 100 U/mL</p> <p>Vial: 100 U/mL</p>

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p>should be infused immediately (within 5 to 10 minutes) before a meal</p> <p>IV: infuse at a concentration of 0.05 to 1.0 U/mL</p>	<p>CSII: approximately 50% of the total dose is usually given as meal-related boluses and the remainder is given as a basal infusion. Pre-meal boluses of should be infused immediately (within 5 to 10 minutes) before a meal</p>	
Insulin glulisine	<p><u>Diabetes:</u> Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously.</p> <p>SC injection: inject 15 minutes before a meal or within 20 minutes of starting a meal</p> <p>CSII: dosage must be individualized</p> <p>IV: infuse at a concentration of 0.05 to 1.0 U/mL</p>	<p>Insulin glulisine has not been studied in pediatric patients with type 1 diabetes younger than 4 years of age and in pediatric patients with type 2 diabetes.</p> <p><u>Type 1 diabetes:</u> Dosage must be individualized. Approved for use in children for SC injections and for CSII by external pump, and intravenously</p> <p>SC injection: 0.5 to 1.0 unit/kg/day administered 15 minutes before a meal or within 20 minutes of starting a meal</p> <p>CSII: dosage must be individualized</p> <p>IV: infuse at a concentration of 0.5 to 1.0 unit/mL</p>	<p>Pen: 100 U/mL</p> <p>Vial: 100 U/mL</p>
Insulin lispro	<p><u>Diabetes:</u> Dosage must be individualized. May be administered via SC injection and CSII by external pump.</p> <p>SC injection, CSII by external pump: 0.5 to 1 unit/kg/day; inject within 15 minutes before or immediately after a meal</p>	<p>Insulin lispro has not been studied in pediatric patients with type 1 diabetes younger than 3 years of age and in pediatric patients with type 2 diabetes.</p> <p><u>Diabetes:</u> Dosage must be individualized. May be administered via SC injection and CSII by external pump.</p> <p>SC injection, CSII by external pump: 0.5 to 1 unit/kg/day; inject within 15 minutes before or immediately after a meal</p>	<p>Cartridge: 100 U/mL</p> <p>Pen: 100 U/mL</p> <p>Vial: 100 U/mL</p>
Short-Acting Insulins			
Insulin regular, human	<p><u>Diabetes:</u> Dosage must be individualized.</p>	Insulin regular, human has not been studied in pediatric	Inhalation powder (Afrezza®):

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p>May be administered via SC injection, via inhalation, and intravenously.</p> <p>Inhalation: Initial (insulin-naïve), 4 units with each meal; dose must be individualized based on response or conversion from other formulations; for doses greater than 8 units, multiple cartridges will be needed</p>	<p>patients with type 1 diabetes younger than 2 years of age in pediatric patients with type 2 diabetes.</p> <p>Diabetes: Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously.</p>	<p>4 units/cartridge 8 units/cartridge 12 units/cartridge</p> <p>Vial: 100 U/mL 500 U/mL</p>
Intermediate-Acting Insulins			
NPH, human insulin isophane	<p>Diabetes: Dosage must be individualized. May be administered via SC injection.</p> <p>SC injection: 0.5 to 1 units/kg/day; administer in 2 divided daily doses and within 60 minutes of a meal</p>	<p>NPH, human insulin isophane has not been studied in pediatric patients younger than 12 years of age.</p> <p>Diabetes: Dosage must be individualized. May be administered via SC injection.</p> <p>SC injection: 0.5 to 1 units/kg/day; administer in 2 divided daily doses and within 60 minutes of a meal</p>	<p>Pen: 300 U/3 mL</p> <p>Vial: 100 U/mL</p>
Long-Acting Insulins			
Insulin degludec	<p>Diabetes: Dosage must be individualized. May be administered via SC injection.</p> <p>SC injection (type 1 diabetes): administer QD</p> <p>SC injection (type 2 diabetes): 10 units once daily</p>	<p>Insulin degludec has not been studied in pediatric patients younger than 1 year of age.</p> <p>Diabetes: Dosage must be individualized. May be administered via SC injection.</p> <p>SC injection: administer QD</p>	<p>Pen: 300 U/3 mL 600 U/3 mL</p>
Insulin detemir	<p>Diabetes: Dosage must be individualized. May be administered via SC injection.</p> <p>SC injection (type 1 diabetes): administer QD or BID</p> <p>SC injection (type 2 diabetes): 10 units once daily in the evening or divided into a twice daily regimen</p>	<p>Insulin detemir has not been studied in pediatric patients younger than 2 years of age with type 1 diabetes and pediatric patients with type 2 diabetes.</p> <p>Type 1 diabetes: Dosage must be individualized. May be administered via SC injection.</p> <p>SC injection: administer QD or BID</p>	<p>Pen: 300 U/3 mL</p> <p>Vial: 100 U/mL</p>
Insulin glargine, human recombinant analog	<p>Diabetes: Dosage must be individualized. May be administered via SC injection.</p>	<p>Insulin glargine, human recombinant analog has not been studied in pediatric patients younger than 6 years</p>	<p>Pen: 300 U/3 mL (Lantus Solostar®) 450U/1.5 mL</p>

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p>SC injection (Lantus®): administer QD at the same time every day; maintenance, 2 to 100 units/day</p> <p>For patients controlled on Lantus®, expect a higher daily dose of Toujeo®.</p> <p>SC injection (Toujeo®): administer QD at the same time every day; maintenance, 1 to 80 units/day</p>	<p>of age with type 1 diabetes and pediatric patients with type 2 diabetes.</p> <p><u>Type 1 diabetes:</u> Dosage must be individualized. May be administered via SC injection.</p> <p>SC injection: administer QD at the same time every day; maintenance, 2 to 100 units/day</p>	<p>(Toujeo Solostar®)</p> <p>Vial: 100 U/mL (Lantus®)</p>
Combination Insulins (Intermediate-Acting and Rapid-Acting)			
<p>Insulin aspart protamine and insulin aspart</p>	<p><u>Diabetes:</u> Dosage must be individualized. May be administered via SC injection.</p> <p>SC injection: fixed ratio insulins are typically dosed on a BID basis (i.e., before breakfast and supper) with each dose intended to cover two meals or a meal and snack. May be injected within 15 minutes of meal initiation.</p>	<p>Safety and efficacy have not been established in pediatric patients.</p>	<p>Pen: 100 U (70-30)/mL</p> <p>Vial: 100 U (70-30)/mL</p>
<p>Insulin lispro protamine and insulin lispro</p>	<p><u>Diabetes Mellitus:</u> Dosage must be individualized. May be administered via SC injection.</p> <p>May be injected within 15 minutes of meal initiation.</p>	<p>Safety and efficacy have not been established in pediatric patients.</p>	<p>Pen: 100 U (50-50)/mL 100 U (75-25)/mL</p> <p>Vial: 100 U (50-50)/mL 100 U (75-25)/mL</p>
Combination Insulins (Intermediate-Acting and Short-Acting)			
<p>NPH, human insulin isophane and insulin regular, human</p>	<p><u>Diabetes:</u> Dosage must be individualized. May be administered via SC injection.</p>	<p>NPH, human insulin isophane and insulin regular, human has not been studied in pediatric patients younger than 12 years of age.</p> <p><u>Diabetes:</u> Dosage must be individualized. May be administered via SC injection.</p>	<p>Pen: 100 U (70-30)/mL</p> <p>Vial: 100 U (70-30)/mL</p>

BID=twice daily, CSII=Continuous Subcutaneous Insulin Infusion, IV=intravenous, QD=once daily, SC=subcutaneous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the insulins are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Insulins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rapid-Acting and Short-Acting Insulin: Type 1 Diabetes Mellitus				
<p>Home et al.³⁴ (2006)</p> <p>Insulin aspart before meals and NPH insulin QD or BID</p> <p>vs</p> <p>regular insulin (REG) before meals and NPH insulin QD or BID</p> <p>Insulin doses were adjusted to achieve target FPG and bedtime glucose 5.0 to 8.0 mmol/L and PPG <10.0 mmol/L.</p>	<p>ES, MC, MN, OL, PG, RCT</p> <p>Patients ≥18 years of age with type 1 diabetes for at least 2 years on insulin for at least 1 year before inclusion, HbA_{1c} ≤11.0%, BMI ≤35 kg/m²</p>	<p>N=753</p> <p>36 months</p>	<p>Primary: HbA_{1c}, hypoglycemia, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: At the end of the original six month study, HbA_{1c} decreased in the insulin aspart group, with a statistically significant difference of -0.12 (95% CI, -0.22 to -0.03; P<0.02). At 30 months during the extension period, the difference of -0.16 in HbA_{1c} was maintained (95% CI, -0.32 to -0.01; P<0.035). At 30 months, mean HbA_{1c} was significantly lower in the insulin aspart group compared to the REG group after adjustment for the rate of hypoglycemic episodes and baseline HbA_{1c} (P<0.001).</p> <p>The RR estimate for major hypoglycemia was similar in both treatment groups at 36 months (RR, 1.0; 95% CI, 0.72 to 1.39; P value not significant). The proportion of patients reporting major hypoglycemia decreased from 16% in the first six months to 3% in the last six months in the insulin aspart group. The frequency of patients reporting major hypoglycemia also decreased in the REG group from 17 to 2%. There were no significant differences between groups in regards to major nocturnal hypoglycemia (RR, 0.89; 95% CI, 0.64 to 1.24; P value not significant).</p> <p>The proportion of patients experiencing adverse events during the treatment period was similar in both treatment groups (P value not reported).</p> <p>Secondary: Not reported</p>
<p>Raskin et al.³⁵ (2000)</p> <p>Insulin aspart before meals and NPH insulin QD to BID</p>	<p>MC, OL, RCT</p> <p>Type 1 diabetes patients with an HbA_{1c} ≤11.0%, baseline HbA_{1c} 7.9% in the insulin</p>	<p>N=882</p> <p>6 months (with 6 month extension period)</p>	<p>Primary: Effect on eight-point blood glucose measurements and HbA_{1c} at six and 12 months</p>	<p>Primary: At six and 12 months, mean PPG (90 minutes postmeal) was significantly lower with insulin aspart compared to REG (P<0.05).</p> <p>At six months, mean pre-prandial lunch and dinner blood glucose levels were significantly lower with insulin aspart when compared to REG (P<0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>regular insulin before meals and NPH insulin QD to BID</p> <p>Doses of insulin were titrated to achieve FPG of 90 to 144 mg/dL, PPG ≤180 mg/dL and 2:00 AM blood glucose of 90 to 144 mg/dL.</p>	<p>aspart group and 7.95% in the REG group; patients were excluded if they had impaired hepatic, renal, or cardiac function; other exclusions included recurrent hypoglycemia, proliferative retinopathy, or total daily insulin requirement ≥1.4 units/kg</p>		<p>Secondary: Not reported</p>	<p>At 12 months, only pre-prandial dinner blood glucose levels were significantly lower with insulin aspart (P<0.05).</p> <p>At six months, HbA_{1c} was significantly lower with insulin aspart (7.78%) when compared to REG (7.93%; P=0.005).</p> <p>At 12 months, HbA_{1c} was significantly lower with insulin aspart (7.78%) when compared to REG (7.91%; P=0.005).</p> <p>Mean NPH dose increased significantly with insulin aspart compared to REG (0.314 vs 0.296 U/kg; P=0.011).</p> <p>Similar rates of hypoglycemia were observed in both treatment groups.</p> <p>Secondary: Not reported</p>
<p>Mathiesen et al.³⁶ (2007)</p> <p>Insulin aspart before meals and NPH insulin QD to QID</p> <p>vs</p> <p>regular insulin before meals and NPH insulin QD to QID</p> <p>Doses were titrated to achieve target goals FPG 4.1 to 6.1 mmol/L, PPG<7.5</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥18 years of age with insulin-treated type 1 diabetes for ≥12 months, either pregnant with a singleton pregnancy (gestational age ≤10 weeks) or planning to become pregnant, HbA_{1c} ≤8.0%</p>	<p>N=412</p> <p>28 months</p>	<p>Primary: Major hypoglycemia during pregnancy</p> <p>Secondary: HbA_{1c}, self-measured eight-point plasma glucose profile, maternal adverse events, obstetric complications, diabetes complications</p>	<p>Primary: The rates of major maternal hypoglycemia were lower in patients taking insulin aspart than patients taking REG. There was a 28% risk reduction for major hypoglycemia (RR, 0.720; 95% CI, 0.36 to 1.46; P value not reported) and a 52% risk reduction for major nocturnal hypoglycemia (RR, 0.48; 95% CI, 0.20 to 1.14; P value not reported) for patients taking insulin aspart than patients taking REG. However, this did not reach statistical significant.</p> <p>Secondary: Treatment with insulin aspart was as effective as treatment with REG in regards to HbA_{1c} (mean difference, -0.04%; 95% CI, -0.18 to 0.11; P value not significant) during the second and third trimester (mean difference, -0.08%; 95% CI, -0.23 to 0.06; P value not significant).</p> <p>Overall eight-point plasma glucose profiles were similar between treatment groups during the second and third trimesters. PPG levels were consistently lower in the insulin aspart group following breakfast than the REG group during the first trimester (P=0.044) and the third trimester (P=0.0007). However, there was no difference in PPG after breakfast during the second</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mmol/L, and HbA _{1c} <6.5%.				<p>trimester (P=0.153).</p> <p>Both treatments were well tolerated and the adverse event profiles were similar between both groups. The frequency and profile of obstetric complications were similar between treatments with the most frequent complications being preeclampsia, threatened preterm labor, prolonged labor, and unplanned cesarean section. Treatment groups were not different in regards to changes in vital signs, physical examinations parameters, electrocardiograms, or clinical laboratory findings (P values were not reported).</p>
<p>Garg et al.³⁷ (2005)</p> <p>Insulin glulisine before morning and evening meals and insulin glargine QD</p> <p>vs</p> <p>insulin glulisine after morning and evening meals and insulin glargine QD</p> <p>vs</p> <p>regular insulin before morning and evening meals and insulin glargine QD</p> <p>Prandial insulin doses were</p>	<p>MC, OL, PG, RCT</p> <p>Patients with type 1 diabetes on insulin therapy for >1 year, baseline HbA_{1c} 7.7% for both insulin glulisine treatment groups and 7.6% for the REG group</p>	<p>N=860</p> <p>12 weeks</p>	<p>Primary: Effect on HbA_{1c}, rate of hypoglycemia, and insulin dose</p> <p>Secondary: Not reported</p>	<p>Primary: HbA_{1c} reductions for insulin glulisine administered after meals (-0.11%) did not differ significantly from REG (-0.13%; P=0.6698).</p> <p>HbA_{1c} reductions for insulin glulisine administered before meals (-0.26%) were significantly lower than REG (-0.13%; P=0.0234).</p> <p>HbA_{1c} reductions for insulin glulisine administered before meals (-0.26%) were significantly lower than insulin glulisine administered after meals (-0.11%; P=0.0062).</p> <p>No significant differences were observed in the rates of symptomatic hypoglycemia (all and severe cases) between pre- and postmeal insulin glulisine and REG (P>0.05).</p> <p>Change in total insulin dose from baseline was significantly higher in the REG group (2.35 U) compared to the premeal insulin glulisine group (0.04 U; P=0.014).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
adjusted to achieve PPG of 120 to 160 mg/dL.				
<p>Dreyer et al.³⁸ (2005)</p> <p>Insulin glulisine before meals and insulin glargine HS</p> <p>vs</p> <p>insulin lispro before meals and insulin glargine HS</p> <p>Insulin doses were adjusted to achieve PPG of 120 to 160 mg/dL.</p>	<p>MC, OL, PG, RCT</p> <p>Patients with type 1 diabetes on insulin therapy for >1 year, baseline HbA_{1c} 7.6% for both treatment groups</p>	<p>N=672</p> <p>26 weeks</p>	<p>Primary: Effect on HbA_{1c}, rate of hypoglycemia, effect on self-monitored blood glucose and insulin dose</p> <p>Secondary: Not reported</p>	<p>Primary: There was a comparable decrease in HbA_{1c} between the insulin glulisine and insulin lispro groups (-0.14% for both groups; P value NS).</p> <p>The incidences of all hypoglycemic events (nocturnal and severe) were similar between the two treatment groups.</p> <p>Self-monitored blood glucose levels were similar in both treatment groups in regards to pre- and postprandial, bedtime and nocturnal blood glucose levels.</p> <p>There was a significant increase in total insulin dose in the insulin lispro group (1.01 units) compared to the insulin glulisine group (-0.86 units; P=0.0123).</p> <p>There was no significant difference in change in rapid-acting insulin dose between treatment groups.</p> <p>Rates of hypoglycemia were similar in both treatment groups. Rates of adverse events were also similar among the two treatment groups.</p> <p>Secondary: Not reported</p>
<p>Philotheou et al.³⁹ (2011)</p> <p>Premeal insulin glulisine</p> <p>vs</p> <p>premeal insulin lispro</p>	<p>MC, NI, OL, PG, RCT</p> <p>Patients 4 to 17 years of age with type 1 diabetes for ≥1 year with HbA_{1c} between 6.0 to 11.0% who were receiving</p>	<p>N=570 (efficacy endpoints)</p> <p>N=572 (safety endpoints)</p> <p>26 weeks (plus a 24-</p>	<p>Primary: Change in HbA_{1c} from baseline at endpoint (study did not define “endpoint”)</p> <p>Secondary: Proportion of patients who</p>	<p>Primary: The adjusted mean change in HbA_{1c} from baseline to endpoint was 0.10±0.08% with insulin glulisine and 0.16±0.07% with insulin lispro. The difference between the two groups was -0.06% (95% CI, -0.24 to 0.12; P value not reported), showing non-inferiority of insulin glulisine compared to insulin lispro based on the prespecified non-inferiority margin of 0.4%.</p> <p>Secondary: At baseline, 33.2 and 33.3% of patients had HbA_{1c} at goal in the insulin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>All patients received NPH BID or insulin glargine QD.</p> <p>Rapid-acting and basal insulin doses were titrated to achieve age-specific FPG goal of 100 to 140 mg/dL (<8 years old) or 90 to 140 mg/dL (≥8 years old) and PPG goal of 120 to 180 mg/dL (<8 years old) or 100 to 160 mg/dL (≥8 years old) using blood-referenced blood glucose meters.</p>	<p>insulin therapy for ≥1 year with NPH insulin or insulin glargine as basal insulin</p>	<p>hour follow-up period)</p>	<p>reached target HbA_{1c}, change in HbA_{1c} from baseline at 12 and 26 weeks, self-monitored FPG, PPG and pre-prandial glucose, insulin doses, symptomatic hypoglycemia between 12 and 26 weeks and safety</p>	<p>glulisine and insulin lispro groups, respectively. At endpoint, the percentage of patients with HbA_{1c} at goal was 38.4% with insulin glulisine and 32.0% with insulin lispro (P=0.039).</p> <p>Change in HbA_{1c} with insulin glulisine and insulin lispro was -0.01±0.07% and -0.03±0.06% at 12 weeks and 0.08±0.08% and 0.17±0.08% at 26 weeks, respectively (P values not reported).</p> <p>At endpoint, self-monitored FPG was lower in the insulin glulisine group compared to the insulin lispro group (158.0±3.8 vs 170.5±3.7 mg/dL; P=0.014). Baseline FPG, PPG and pre-prandial glucose as well as endpoint PPG and pre-prandial glucose were comparable between the two groups.</p> <p>Total daily insulin doses increased by 0.01±0.01 units/kg with insulin glulisine and by 0.05±0.01 units/kg with insulin lispro (P=0.0045).</p> <p>The monthly rate of symptomatic hypoglycemia per patient was 3.10±4.33 and 2.91±4.35 with insulin glulisine and insulin lispro, respectively (P value not reported). No difference was seen with the two groups in severe, nocturnal or severe nocturnal symptomatic hypoglycemia.</p> <p>The frequency and type of treatment-emergent adverse events or serious adverse events were similar between the treatment groups.</p>
<p>van Bon et al.⁴⁰ (2011)</p> <p>Insulin glulisine vs insulin aspart vs insulin lispro</p>	<p>MC, OL, RCT, XO</p> <p>Patients ≥18 years of age with type 1 diabetes treated with insulin for ≥2 years and continuous SC insulin infusion for ≥6 months, requiring ≤90</p>	<p>N=256</p> <p>39 weeks (13 weeks of treatment period for each study medication)</p>	<p>Primary: Unexplained hyperglycemia (>300 mg/dL) and/or perceived infusion set occlusion</p> <p>Secondary: Unexplained hyperglycemia, perceived</p>	<p>Statistical significant was defined as P <0.025 in this study.</p> <p>Primary: Percentage of patients with at least one unexplained hyperglycemia and/or perceived infusion set occlusion was comparable between insulin glulisine and insulin aspart (68.4 vs 62.1%; P=0.04) and between insulin glulisine and insulin lispro (68.4 vs 61.3%; P=0.03).</p> <p>Secondary: Percentage of patients reporting at least one unexplained hyperglycemia was similar when comparing insulin glulisine (61.3%) to insulin aspart (55.9%; P=0.08) and insulin lispro (56.3%; P=0.11).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin doses were titrated to achieve PPG <180 mg/dL and pre-prandial glucose between 90 to 130 mg/dL.</p>	<p>units/day of insulin, with HbA_{1c} <8.5% and BMI<35 kg/m²</p>		<p>infusion set occlusion, HbA_{1c}, proportion of patients with HbA_{1c} <7.0%, seven-point plasma glucose profiles, hypoglycemic episodes, episodes of asymptomatic ketonemia and ketoacidosis, insulin doses, time to infusion set change, infusion site reactions and serious adverse reactions</p>	<p>No significant difference was seen in the percentage of patients with at least one perceived infusion set occlusion between insulin glulisine and insulin aspart (32.8 vs 27.0%; P=0.08) and between insulin glulisine and insulin lispro (32.8 vs 27.0; P=0.06).</p> <p>HbA_{1c} remained stable from baseline at the end of treatment period with all three insulin groups, with no significant differences seen among groups.</p> <p>Similar percentage of patients achieved HbA_{1c} <7.0% in the insulin glulisine, insulin aspart and insulin lispro groups (28, 31 and 30%, respectively; P values not reported).</p> <p>The seven-point plasma glucose profiles were similar among all three groups at baseline. At the end of treatment, after-lunch glucose was higher with insulin glulisine compared to insulin aspart (166.1 vs 155.5 mg/dL; P=0.021), and midnight glucose was higher with insulin lispro compared to insulin glulisine (159.4 vs 148.1 mg/dL; P=0.018).</p> <p>The overall rate of symptomatic hypoglycemia per patient-year was higher with insulin glulisine (73.8) compared to insulin aspart (65.0; P=0.008) and insulin lispro (62.7; P<0.001).</p> <p>The monthly rate of significant hyperketonemia and/or hyperketonemia at risk for ketosis was higher with insulin glulisine (0.14) compared to insulin aspart (0.06; P=0.01) and insulin lispro (0.06; P=0.02). One patient was hospitalized for diabetic ketoacidosis while receiving insulin glulisine.</p> <p>Insulin doses remained stable throughout the study. No significant differences were seen among the three groups in time to infusion set change, frequency of infusion site reactions and serious adverse reactions. No death was reported.</p>
<p>Rave et al.⁴¹ (2006)</p>	<p>4-way XO, OL, RCT, single-dose</p>	<p>N=21 4</p>	<p>Primary: Blood glucose exposure and</p>	<p>Primary: Blood glucose exposure within two hours after the start of a meal was significantly lower with insulin glulisine than with REG (279 vs 344</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Premeal insulin glulisine (2 minutes prior to a standardized 15-minute meal)</p> <p>vs</p> <p>postmeal insulin glulisine (15 minutes postmeal)</p> <p>vs</p> <p>premeal regular insulin (30 minutes premeal)</p> <p>vs</p> <p>premeal regular insulin (2 minutes premeal)</p>	<p>Patients 18 to 55 years of age with type 1 diabetes on the same insulin regimen for ≥ 2 months before enrollment, BMI 18 to 32 kg/m², HbA_{1c} <10.0%, serum C-peptide levels ≤ 0.9 ng/mL</p>	<p>treatment periods</p>	<p>excursion at two and six hours following a meal, mean maximum blood glucose concentration, time to reach mean maximum blood glucose concentration</p> <p>Secondary: Not reported</p>	<p>mg·h/dL, respectively; P value not reported). However, at six hours following a meal, blood glucose exposure was not significantly different between both groups (708 vs 770 mg·h/dL, respectively; P value not reported).</p> <p>When insulin glulisine was given immediately prior to a meal and REG 30 minutes prior to the meal, blood glucose control was comparable. Both two- and six-hour blood glucose exposures were well matched. However, treatment with REG resulted in time to maximum blood glucose excursion to occur 43 minutes later compared to insulin glulisine.</p> <p>Postmeal insulin glulisine and REG given immediately premeal produced similar effects on PPG exposure and excursion at two hours after a meal (337 vs 334 mg·h/dL, respectively) and six hours after a meal (777 vs 770 mg·h/dL, respectively; P values not reported).</p> <p>Insulin glulisine was absorbed more rapidly than REG and reached a mean maximum concentration that was almost twice as large as the mean maximum concentration for REG (P value was not reported).</p> <p>In addition, the time to reach maximum concentration for insulin glulisine was half that of REG (P value was not reported).</p> <p>Secondary: Not reported</p>
<p>Anderson et al.⁴² (1997)</p> <p>Insulin lispro before each meal and basal insulin for 3 months</p> <p>vs</p> <p>Regular insulin (REG) before</p>	<p>MC, OL, RCT, XO</p> <p>Patients with type 1 diabetes previously treated with REG, baseline HbA_{1c} 8.5% for both groups</p>	<p>N=1,008</p> <p>6 months</p>	<p>Primary: Effect on postprandial serum glucose (one- and two-hour), HbA_{1c}, and frequency of hypoglycemia</p> <p>Secondary: Effect on insulin dose, frequency</p>	<p>Primary: One-hour postprandial serum glucose rise was significantly lower with insulin lispro compared to REG (12.9 vs 13.9 mmol/L; P<0.001).</p> <p>Two-hour postprandial serum glucose rise was significantly lower with insulin lispro compared to REG (11.2 vs 12.9 mmol/L; P<0.001).</p> <p>There was no difference in HbA_{1c} reduction between the two treatment groups.</p> <p>The rate of hypoglycemia was 12% less during treatment with insulin lispro when compared to REG (P<0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
each meal and basal insulin for 3 months			of premeal and basal insulin injections, and weight	<p>Secondary: A small but significant increase in total insulin dose was observed with insulin lispro when compared to REG (0.71 vs 0.69 U/kg; P<0.001).</p> <p>No significant difference was reported for frequency of premeal injections between the two treatment groups.</p> <p>Significantly less patients on REG required ≥ 2 basal insulin injections compared to insulin lispro (46.4 vs 44.0%; P<0.05).</p> <p>There were no significant differences in weight gain between the two treatment groups.</p> <p>There were no differences in type and frequency of adverse events between the two treatments.</p>
<p>Fairchild et al.⁴³ (2000)</p> <p>Insulin lispro and NPH or Lente insulin for 3 months vs regular insulin (REG) and NPH or Lente insulin for 3 months</p> <p>Insulin doses were titrated to achieve HbA_{1c} 6.0 to 8.0% and preprandial blood glucose levels 4 to 10 mmol/L.</p>	<p>OL, RCT, XO</p> <p>Children 5 to 10 years of age with type 1 diabetes for at least 12 months, prepubertal, on BID insulin, attending the Diabetes Clinics at the New Children's Hospital, Newcastle</p>	<p>N=43</p> <p>6 months</p>	<p>Primary: HbA_{1c}</p> <p>Secondary: Blood glucose levels before and after meals, two-hour PPG excursions, hypoglycemic events</p>	<p>Primary: After three months, change in HbA_{1c} was not significantly different between patients on insulin lispro and patients on REG (mean difference, -0.19±0.63%; P value not reported).</p> <p>Secondary: There were no significant differences in blood glucose levels before or after meals and two-hour PPG excursions. However, the 3 AM blood glucose levels were significantly lower in patients taking REG than in patients taking insulin lispro (mean difference between treatments, -2.35 mmol/L; 95% CI, -3.98 to -0.72; P=0.01).</p> <p>There was no significant difference in the frequency of total hypoglycemic episodes or hypoglycemic episodes with a blood glucose <3 mmol/L between patients taking REG and patients taking insulin lispro (P value was not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Mortensen et al.⁴⁴ (2006)</p> <p>Premeal biphasic insulin aspart (BIAsp) 30 plus NPH insulin at bedtime (HS)</p> <p>vs</p> <p>premeal REG (before lunch and dinner) plus biphasic human insulin (BHI) 30 before breakfast and NPH insulin HS</p> <p>Insulin doses were titrated to achieve target FPG <8 mmol/L and PPG <10 mmol/L.</p>	<p>MN, OL, PG, RCT</p> <p>Adolescents 10 to 17 years of age with type 1 diabetes for at least 18 months</p>	<p>N=167</p> <p>16 weeks</p>	<p>Primary: HbA_{1c}, change in PPG, body weight, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: HbA_{1c} decreased by about -0.2% in both treatment arms at endpoint. There was no significant difference in the change of HbA_{1c} between groups at study endpoint (P=0.62).</p> <p>At 16 weeks, both the biphasic insulin aspart group and REG group had reductions in average PPG (SEM, 0.37 and 0.77, respectively; P=0.47).</p> <p>The increase in body weight was smaller in the biphasic insulin aspart group than the REG group. The difference between groups was significant for males (P=0.007), but not for females.</p> <p>The rates of hypoglycemia during the day and during the night were similar between treatment groups (P value was not reported).</p> <p>Secondary: Not reported</p>
<p>Chen et al.⁴⁵ (2006)</p> <p>Biphasic insulin aspart 30 (BIAsp30) TID, divided in a 30:30:40 ratio for 12 weeks; NPH could also be added at bedtime</p>	<p>OL, RCT, XO</p> <p>Patients ≥18 years of age with type 1 diabetes for ≥12 months, previously treated with soluble human insulin TID plus NPH at bedtime with a total daily dose <1.8 IU/kg,</p>	<p>N=27</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline at end of each 12 week-treatment period, daily seven-point self monitoring of blood glucose</p> <p>Secondary: Hypoglycemia</p>	<p>Primary: Eleven out of 27 patients chose to take bedtime NPH while they were being treated with insulin aspart.</p> <p>Both the biphasic insulin aspart and the REG groups had significant improvement in HbA_{1c} levels from baseline (P<0.01). However, the biphasic insulin aspart group had a significantly greater reduction in HbA_{1c} than that of the REG group (P<0.05). Upon further analysis it was ascertained that most of the between-group difference in HbA_{1c} was driven by the patients who administered bedtime NPH in combination with their TID biphasic insulin aspart.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>REG insulin administered TID plus NPH insulin at bedtime for 12 weeks</p> <p>Doses were titrated to achieve FPG 5.0 to 8.0 mmol/L and PPG 5.0 to 10.0 mmol/L.</p>	<p>BMI <35 kg/m² and HbA_{1c} ≥8.0% during the last 6 months; at 12 weeks, patients were switched to the alternative insulin regimen for another 12 weeks</p>			<p>Both the biphasic insulin aspart and the REG groups had similar results in self monitoring of blood glucose of daytime glycemic control. However, the biphasic insulin aspart group had significantly lower blood glucose concentrations at two hours after dinner and at bedtime in comparison to the REG group (P<0.05).</p> <p>Secondary: The rates of hypoglycemia (events/patient-week) were similar among the biphasic insulin aspart and REG group (1.2 vs 0.7, respectively for total events and 0.2 vs 0.2, respectively for nocturnal events; P value not reported).</p>
<p>Rapid-Acting and Short-Acting Insulin Administered By Continuous Subcutaneous Insulin Infusion (CSII): Type 1 Diabetes Mellitus</p>				
<p>Bode et al.⁴⁶ (2002)</p> <p>Insulin aspart (IAsp) administered by CSII via external pump</p> <p>vs</p> <p>insulin lispro administered by CSII via external pump</p> <p>vs</p> <p>regular insulin (BR) administered by CSII via external pump</p>	<p>MC, OL, PG, RCT</p> <p>Patients 18 to 71 years of age with type 1 diabetes with fasting C-peptide <0.5 ng/mL who had been treated with CSII therapy continuously for the previous 3 months</p>	<p>N=146</p> <p>16 weeks</p>	<p>Primary: HbA_{1c}, eight-point self monitoring blood glucose, weight, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: After 16 weeks of treatment, the mean change in HbA_{1c} from baseline was not significantly different among the three groups (0.00%, 0.15%, and 0.18% for the IAsp, BR, and lispro groups, respectively).</p> <p>For the eight-point self monitoring blood glucose evaluation, postprandial values for subjects in the rapid-acting insulin analog groups were improved from baseline values and tended to be lower than those for subjects in the BR group. A few statistically significant differences were observed at week 16 between the treatment groups: dinner +90 minutes, the blood glucose value for the IAsp group was lower than those for BR and lispro groups (P=0.019); at 2:00 A.M., the blood glucose value for the BR group was lower than those for IAsp and lispro groups (P=0.002).</p> <p>Mean weight did not significantly increase or decrease during the study among the treatment groups.</p> <p>Similar numbers of subjects (≥90%) in each treatment group reported one or more minor hypoglycemic episodes. The rate of confirmed hypoglycemia was not significantly different between treatment groups. The rate of confirmed nocturnal hypoglycemia for the IAsp group was lower than that for the BR group and similar to that of the lispro group. No</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>major nocturnal hypoglycemic episodes occurred during the study.</p> <p>Secondary: Not reported</p>
<p>Weinzimer et al.⁴⁷ (2008)</p> <p>Insulin aspart administered by CSII via external pump</p> <p>vs</p> <p>insulin lispro administered by CSII via external pump</p>	<p>MC, OL, PG, RCT</p> <p>Patients 3 to 18 years of age with type 1 diabetes for ≥ 1 year and HbA_{1c} $\leq 10.0\%$ who were being treated with either insulin aspart or insulin lispro by CSII for ≥ 3 months</p>	<p>N=298</p> <p>16 weeks</p>	<p>Primary: HbA_{1c} at week 16</p> <p>Secondary: FPG, eight-point self monitoring blood glucose, weight, hypoglycemia</p>	<p>Primary: At study end point, the mean HbA_{1c} values were 7.9% and 8.1% (last observation carried forward) for insulin aspart and insulin lispro, respectively. The change in HbA_{1c} from baseline to week 16 was -0.15% in the insulin aspart group and -0.05% in the insulin lispro group (95% CI, -0.27 to 0.07).</p> <p>After 16 weeks, 59.7% of patients in the insulin aspart group and 43.8% of the patients in the insulin lispro group achieved American Diabetes Association age-specific recommendations for HbA_{1c} (P=0.040).</p> <p>Secondary: After 16 weeks, mean FPG were similar among the treatment groups (insulin aspart 166.5 mg/dl; lispro 180.2 mg/dl; P=0.113).</p> <p>The eight-point self monitoring blood glucose profiles collected before weeks 0 and 16 showed a similar pattern for both treatment groups. No significant differences between treatment groups in mean self monitoring blood glucose values were observed at any of the eight time points at week 16.</p> <p>Mean body weight increased from baseline for both treatment groups during the trial, but was comparable between treatment groups (insulin aspart 1.8 kg; insulin lispro 1.6 kg; P=0.387).</p> <p>Rates of minor and major hypoglycemic episodes were similar between the two treatment groups. A similar percentage of patients reported at least one major hypoglycemic event during the study period (9.6 and 8.0% in the insulin aspart and insulin lispro groups, respectively). Rates of nocturnal hypoglycemic events were also similar between the treatment groups.</p>
<p>Colquitt et al.⁴⁸ (2003)</p>	<p>MA</p> <p>Analysis of 6</p>	<p>N=577</p> <p>Duration</p>	<p>Primary: Effect in HbA_{1c}, insulin dose,</p>	<p>Primary: Significant improvement in HbA_{1c} of -0.26% (95% CI, -0.47 to -0.06; P=0.01) was observed with insulin lispro compared to REG.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Rapid-acting insulin analogs administered by CSII</p> <p>vs</p> <p>regular insulin administered by CSII</p>	<p>randomized trials that compared rapid-acting insulin analogs vs REG in the treatment of patients with diabetes using continuous infusions; trials less than 10 weeks in duration were excluded</p>	<p>varied</p>	<p>weight change, patient preference, quality of life and adverse events</p> <p>Secondary: Not reported</p>	<p>The differences in HbA_{1c} from baseline between insulin aspart, REG, or insulin lispro were not significant.</p> <p>No significant difference in insulin dose was reported between treatment groups.</p> <p>No significant difference in weight was reported between treatment groups.</p> <p>Two studies reported patient preference to short-acting insulin analogs. One study found no difference in satisfaction between treatment groups and one study found greater patient satisfaction towards short-acting insulin analogs.</p> <p>No difference in frequency of severe hypoglycemic events was reported between treatment groups.</p> <p>Secondary: Not reported</p>
<p>Rapid-Acting and Short-Acting Insulin: Type 2 Diabetes Mellitus</p>				
<p>McSorley et al.⁴⁹ (2002)</p> <p>Biphasic insulin aspart (BIAsp) 30 BID for 2 weeks</p> <p>vs</p> <p>biphasic human insulin (BHI) 30 BID for 2 weeks</p> <p>Patients were XO to other insulin regimen after 2</p>	<p>2-period, DB, RCT, XO</p> <p>Patients 40 to 75 years of age with type 2 diabetes for at least 1 year, had been on BID biphasic human insulin 30 for at least 6 months</p>	<p>N=13</p> <p>4 weeks</p>	<p>Primary: AUC during two hours following insulin administration at dinner and breakfast</p> <p>Secondary: Maximum serum insulin concentration after two injections; time to reach peak serum insulin</p>	<p>Primary: The AUC two hours following insulin administration was significantly greater for biphasic insulin aspart 30 than for biphasic human insulin 30 after dinner and breakfast (P<0.05).</p> <p>Secondary: Biphasic insulin aspart 30 reached a maximum concentration that was 18% higher after dinner and 35% higher after the following day's breakfast than that of biphasic human insulin 30 (P<0.05 for both values).</p> <p>The time taken to reach peak serum insulin concentrations was one hour earlier after breakfast and 45 minutes earlier after dinner in the biphasic insulin aspart 30 group compared to the biphasic human insulin 30 group. However, the only measure to reach statistical significance was after breakfast (P<0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks of initial randomized insulin regimen.			concentrations; four-hour glucose excursion following dinner, breakfast, and lunch; glucose maximum concentration after dinner, breakfast, and lunch; time taken to reach glucose maximum concentration values	<p>Serum glucose excursions were significantly lower in the biphasic insulin aspart 30 group than the biphasic human insulin 30 group after dinner ($P<0.05$) and after breakfast ($P<0.05$). However, serum glucose excursion after lunch was significantly higher in the biphasic insulin aspart 30 group than the biphasic human insulin 30 group ($P<0.05$).</p> <p>Following breakfast, glucose maximum concentration was significantly lower and time to reach glucose maximum concentration was significantly earlier with biphasic insulin aspart 30 than biphasic human insulin 30 ($P<0.05$ for both measures).</p> <p>Both insulins were well-tolerated and had comparable adverse events. There were no major hypoglycemic episodes or serious adverse events reported.</p>
<p>Bretzel et al.⁵⁰ (2004)</p> <p>Insulin aspart before meals and NPH insulin QD (if needed)</p> <p>vs</p> <p>regular insulin before meals and NPH insulin QD (if needed)</p> <p>vs</p> <p>NPH/REG insulin 70/30 mix QD to BID</p>	<p>MC, OL, PG, RCT</p> <p>Adult (≥ 35 years of age) type 2 diabetes with $HbA_{1c} \leq 10.0\%$, baseline HbA_{1c} 7.82% for insulin aspart, 7.83% for REG and 7.78% for the premixed insulin</p>	<p>N=231</p> <p>12 weeks</p>	<p>Primary: Equivalence of the primary efficacy endpoint—effect on HbA_{1c}</p> <p>Secondary: Not reported</p>	<p>Primary: Insulin aspart reduced HbA_{1c} by $-0.91 \pm 1.00\%$, while REG reduced HbA_{1c} by $-0.73 \pm 0.87\%$ and premixed insulin reduced HbA_{1c} by $-0.65 \pm 1.10\%$.</p> <p>Insulin aspart was found not to be statistically equivalent to REG ($P=0.025$) or the premixed insulin formulation ($P=0.092$). Significance level for P was set at 0.0083.</p> <p>The proportion of patients reporting an adverse event was comparable in all three treatment groups.</p> <p>The proportion of patients that experienced a hypoglycemic event (41% for insulin aspart and REG and 30% for premixed insulin) was not statistically different.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin doses were titrated to achieve blood glucose levels of 80 to 110 mg/dL.</p>				
<p>Niskanen et al.⁵¹ (2004)</p> <p>Insulin aspart 30% and insulin aspart protamine 70% administered via proprietary pen for 12 weeks</p> <p>vs</p> <p>insulin lispro 25% and insulin lispro protamine 75% administered via proprietary pen for 12 weeks</p>	<p>MC, OL, RCT, XO</p> <p>Patients with type 2 diabetes previously treated with insulin with HbA_{1c} <12.0%, baseline HbA_{1c} for the whole sample size was 8.5%</p>	<p>N=137</p> <p>24 weeks</p>	<p>Primary: Effect on HbA_{1c} and seven-point blood glucose levels</p> <p>Secondary: Patient satisfaction with the pen devices</p>	<p>Primary: HbA_{1c} reduction was comparable between the two treatment groups.</p> <p>The seven-point blood glucose profile was comparable at each time point and there was no significant difference between the two treatment groups.</p> <p>Secondary: Significantly more patients preferred the insulin aspart pen device compared to the insulin lispro pen device (P<0.005).</p> <p>The incidence of reported adverse events was similar between treatment groups.</p>
<p>Dailey et al.⁵² (2004)</p> <p>Insulin glulisine before meals BID (AM and PM) and NPH insulin BID</p> <p>vs</p> <p>regular insulin before meals BID (AM and PM) and NPH insulin BID</p>	<p>MC, OL, PG, RCT</p> <p>Patients with type 2 diabetes on continuous insulin therapy for ≥6 months, baseline HbA_{1c} 7.58% for insulin glulisine and 7.52% for REG</p>	<p>N=876</p> <p>26 weeks</p>	<p>Primary: Effect on HbA_{1c}, rate of hypoglycemia, effect on self-monitored blood glucose and insulin dose</p> <p>Secondary: Not reported</p>	<p>Primary: There was a small, but significantly greater decrease in HbA_{1c} observed in the insulin glulisine group compared to the REG group (-0.46 vs -0.30%; P=0.0029).</p> <p>No significant differences were observed in either group in the incidence of hypoglycemia.</p> <p>Significantly lower two-hour PPG (breakfast and dinner) was observed in the insulin glulisine group compared to the REG group (P<0.05).</p> <p>There was no significant difference in total daily insulin doses between the two treatment groups throughout the study.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin doses were adjusted to achieve PPG 120 to 160 mg/dL.</p>				<p>Secondary: Not reported</p>
<p>Rayman et al.⁵³ (2007)</p> <p>Insulin glulisine and NPH insulin BID, in addition to current oral antidiabetic agents</p> <p>vs</p> <p>Regular insulin and NPH insulin BID, in addition to current oral antidiabetic agents</p> <p>Insulin glulisine and regular doses were adjusted to achieve target PPG 120 to 160 mg/dL.</p> <p>NPH insulin was titrated to achieve FPG 90 to 120 mg/dL.</p>	<p>MC, MN, OL, PG, RCT</p> <p>Patients aged ≥ 18 years of age with type 2 diabetes on >6 months of continuous insulin treatment prior to study entry, HbA_{1c} 6.0 to 11.0%, ability and willingness for self monitoring of blood glucose</p>	<p>N=892</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c}, adverse events</p> <p>Secondary: Difference in the change of HbA_{1c} at 12 and 26 weeks between insulin glulisine and REG, self-monitored seven-point blood glucose profile, symptomatic hypoglycemia, insulin dose</p>	<p>Primary: HbA_{1c} decreased from baseline to study endpoint in both the insulin glulisine and REG groups. HbA_{1c} in the insulin glulisine group decreased from 7.58\pm0.90% to 7.25\pm0.95% and from 7.50\pm0.89% to 7.19\pm0.90% in the REG group (P value not reported). No difference between groups was seen in the proportion of patients achieving HbA_{1c} levels $\leq 7.0\%$ (P=0.8962).</p> <p>There was no between-treatment difference in the frequency and type of treatment emergent adverse events observed (P value not reported).</p> <p>Secondary: There was no between-treatment difference in change in HbA_{1c} for insulin glulisine and REG at 12 weeks and study endpoint (P=0.3573 and P=0.5726, respectively).</p> <p>At study endpoint, glucose values were significantly lower two hours postbreakfast with insulin glulisine compared to REG (P<0.001).</p> <p>There were no noteworthy differences between both treatment groups in the frequencies and monthly rates of all symptomatic hypoglycemia. However, the frequencies and monthly rates of severe symptomatic hypoglycemia were lower in the insulin glulisine group than the REG group. Patients taking insulin glulisine also had fewer reports of nocturnal symptomatic hypoglycemia from month four to treatment end compared to patients taking REG (P=0.029).</p> <p>In terms of insulin doses, there was a larger increase in the short-acting dose with REG than with insulin glulisine (adjusted mean, 4.47 vs 2.95 U, respectively; P=0.0645). Overall, the total daily insulin dose increased slightly more with REG. However, the difference was not significant (P=0.1727).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Rosenstock et al.⁵⁴ (2008)</p> <p>Basal bolus therapy (BBT) (premeal insulin lispro and insulin glargine HS)</p> <p>vs</p> <p>premeal premixed therapy (PPT) (lispro mix 50/50 TID)</p>	<p>MC, NI, OL, RCT</p> <p>Patients with type 2 diabetes</p>	<p>N=374</p> <p>24 weeks</p>	<p>Primary: HbA_{1c}, percentage of patients achieving HbA_{1c} <7.0%, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: HbA_{1c} was reduced significantly from baseline in both treatment groups (P<0.0001). At 24 weeks, HbA_{1c} was lower with basal bolus therapy compared to premeal premixed therapy (6.78 vs 6.95%, respectively; P=0.021). The difference between treatment groups was -0.22% (90% CI, -0.38 to -0.07; P value not reported).</p> <p>The percentage of patients achieving an HbA_{1c} <7.0% was 54 vs 69% in the premeal premixed therapy and basal bolus therapy groups, respectively (P=0.009).</p> <p>Rates of hypoglycemia were similar between both treatment groups.</p> <p>Secondary: Not reported</p>
<p>Tack et al.⁵⁵ (2008)</p> <p>Technosphere® Inhaled Insulin (TI) at four different doses (equivalent to 3.6, 7.3, 10.9, and 14.6 U subcutaneous regular human insulin)</p> <p>vs</p> <p>Technosphere® Powder Placebo</p> <p>All patients received basal insulin glargine.</p>	<p>DB, MC, PC, PRO</p> <p>Adult patients 18 to 80 years of age with type 2 diabetes mellitus poor glycemic control (HbA_{1c} between 7 and 12%) with a minimum of two months of treatment with a stable dose of ≥1 antihyperglycemic agent and/or basal insulin glargine therapy</p>	<p>N=227</p> <p>11 weeks</p>	<p>Primary: Change in HbA_{1c} of each randomized dose from baseline</p> <p>Secondary: PPG, safety</p>	<p>Primary: Mean reductions in HbA_{1c} from baseline were statistically significant for all treatment groups and increased with increasing TI doses. The greatest reduction from Technosphere powder alone was seen in the TI 14.6 U-equivalent group (0.78%).</p> <p>Secondary: TI treatment significantly reduced PPG excursions after a mixed meal. Over the 11-week treatment period, dose-dependent and statistically significant mean reductions from baseline were seen in postprandial AUC_{glucose} at 0 to 300 minutes for the 7.3, 10.9, and 14.6 U-equivalent groups (P≤0.001 for these groups).</p> <p>Patients randomized to the highest TI doses experienced more hypoglycemic events than those randomized to Technosphere powder alone or to the lowest two TI doses. Cough was reported by 10 subjects in the Technosphere powder alone group and by 4 to 12 subjects in the TI groups. Changes in pulmonary function parameters (FVC, FEV₁, and DL_{CO}) were minimal during the study period.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Rosenstock et al.⁵⁶ (2008)</p> <p>Technosphere® Inhaled Insulin</p> <p>vs</p> <p>Technosphere® Powder Placebo</p> <p>Each group in addition to oral antidiabetic (OAD) agents.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Insulin-naïve patients (18 to 80 years of age with diabetes duration of 2 to 12 years), treated with at least one OAD, were on a stable regimen for at least three months before enrollment</p>	<p>N=126</p> <p>12 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to study end</p> <p>Secondary: PPG concentrations after the meal at baseline and after 4, 8, and 12 weeks of treatment, safety</p>	<p>Primary: After 12 weeks of treatment, mean HbA_{1c} decreased by -0.7% with Technosphere insulin and by -0.3% with Technosphere powder (P=0.003) from baselines of 8.0 and 7.8%, respectively.</p> <p>Secondary: Postprandial glucose excursions were reduced by 56% with Technosphere insulin compared with baseline, and maximal postprandial glucose levels were reduced by 43% compared with Technosphere powder.</p> <p>Incidences of hypoglycemia and hyperglycemia were similar for both groups, with no significant between-group differences (P=0.321 and P=0.871, respectively). Coughing episodes were similar in both groups. Pulmonary function outcomes were not considered clinically relevant.</p>
<p>Rosenstock et al.⁵⁷ (2010)</p> <p>Prandial Technosphere inhaled insulin powder plus bedtime insulin glargine</p> <p>vs</p> <p>twice daily premixed biaspart insulin (70% insulin aspart protamine suspension and 30% insulin aspart of rDNA origin).</p>	<p>OL, PG, RCT</p> <p>Adult patients 18 to 80 years of age with type 2 diabetes mellitus poor glycemic control (HbA_{1c} between 7 and 11%) despite insulin therapy, with or without oral antidiabetes drugs</p>	<p>N=677</p> <p>52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to study end</p> <p>Secondary: Change from baseline in plasma glucose concentrations, proportion of patients achieving HbA_{1c} ≤7%, change in FPG, weight, safety</p>	<p>Primary: Mean changes in HbA_{1c} from baseline to week 52 were similar across all analysis populations with all upper 95% CIs <0.4, showing that inhaled insulin is non-inferior to biaspart insulin.</p> <p>Secondary: Mean fasting plasma glucose values at week 52 were 7.8 mmol/L for inhaled insulin plus insulin glargine and 8.7 mmol/L for biaspart insulin. The between-group difference was -1.0 mmol/L (SD 0.3, 95% CI -1.6 to -0.3, P=0.0029).</p> <p>The proportion of patients with HbA_{1c} of 7.0% or less at week 52 was similar between patients on inhaled insulin and insulin glargine (22%) and those on biaspart insulin (27%, P=0.2793). Mean weight gain was significantly lower with inhaled insulin plus insulin glargine 0.9 kg (SD 0.3; 95% CI 0.3 to 1.5) than with biaspart insulin 2.5 kg (0.3, 1.9 to 3.0), with a treatment difference of -1.6 kg (SD 0.4; 95% CI -2.4 to -0.7; P=0.0002).</p> <p>In the safety population, adverse events occurred in 272 patients (84%) on inhaled insulin plus insulin glargine and 296 (89%) of those on biaspart insulin, with hypoglycemia being the most frequent adverse</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Raskin et al.⁵⁸ (2012)</p> <p>Prandial inhaled Technosphere Insulin (TI) vs standard antidiabetes treatment (usual care)</p> <p>Control group of non-diabetic patients also included with no intervention</p>	<p>MC, OL, RCT</p> <p>Patients 18 to 80 years of age with type 1 or type 2 diabetes for at least two years and HbA_{1c} ≥6.6% and ≤12.0%</p>	<p>N=1699</p> <p>2 years</p>	<p>Primary: Change from baseline in pre-bronchodilator FEV₁ at month 24 between the diabetes treatment groups</p> <p>Secondary: Treatment group difference in the incidence of FEV₁ findings (≥15% decline) and change from baseline in FVC, TLC, DL_{CO} and HbA_{1c}</p>	<p>event, occurring in 31% of inhaled insulin patients and 49% of biaspart insulin patients. 103 patients (32%) treated with inhaled insulin plus insulin glargine reported cough compared with 14 (4%) receiving biaspart insulin.</p> <p>Primary: Over two years, small declines from baseline in FEV₁ were observed in all groups, with the smallest change in those without diabetes. The adjusted mean treatment group difference in change in FEV₁ from baseline to month 24 was 0.037 (95% CI, 0.014 to 0.060). The upper limit of the 95% CI for the treatment group difference in FEV₁ change at month 24 was less than the pre-specified non-inferiority margin of 100 mL (50 mL/year), demonstrating non-inferiority with TI over usual care.</p> <p>Secondary: At month 24, the adjusted treatment group difference in mean FVC was small (0.034 l [standard error of the mean 0.0135]). TLC and DL_{CO} treatment group differences were not statistically significant.</p> <p>In all, 42 of 730 (5.75%) patients receiving TI and 27 of 824 (3.28%) receiving usual care had protocol-predefined FEV₁ findings (≥15% decrease from baseline) at last measurement. Treatment group difference (usual care—TI) in the percentage of patients with FEV₁ decline of ≥15% from baseline was -2.48% (95% CI, -4.5578 to 0.3956). Lower bound of 95% CI did not exceed -5%, thereby demonstrating that TI was non-inferior to usual care.</p> <p>Mean (standard deviation) change in HbA_{1c} from baseline to month 24 was comparable between treatment groups.</p> <p>More treatment-emergent adverse events (TEAE) were reported in patients receiving TI (n=729 [79.0%]) than in patients receiving usual care (n=674 [71.0%]); The most common TEAE in both treatment groups was hypoglycemia. Cough, the second most common TEAE, was more frequent with TI than with usual care.</p>
Rapid-Acting and Short-Acting Insulin: Type 1 and Type 2 Diabetes Mellitus				
<p>Vignati et al.⁵⁹ (1997)</p>	<p>MC, OL, RCT, XO</p>	<p>N=707</p>	<p>Primary: Effect on HbA_{1c},</p>	<p>Primary: There was no significant difference in HbA_{1c} reduction between the two</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin lispro and NPH insulin BID before meals for 2 months</p> <p>vs</p> <p>regular insulin and NPH insulin BID before meals for 2 months</p> <p>Doses of both regimens were adjusted to achieve 2-hour postprandial serum glucose ≤ 160.2 mg/dL and fasting serum glucose ≤ 140.0 mg/dL.</p>	<p>Patients with type 1 diabetes and type 2 diabetes previously treated with REG and NPH, baseline HbA_{1c} 8.0% for both groups in patients with type 1 diabetes and 8.1% for both groups in patients with type 2 diabetes</p>	<p>4 months</p>	<p>pre-prandial glucose levels, PPG levels and frequency of hypoglycemia, and insulin dose</p> <p>Secondary: Not reported</p>	<p>treatment groups ($P > 0.648$).</p> <p>Pre-prandial glucose levels did not differ significantly between the two treatment groups for any meal ($P \geq 0.066$) or at bedtime ($P > 0.404$).</p> <p>PPG was significantly lower with insulin lispro compared to REG for the morning meal (8.6 vs 9.8 mmol/L; $P < 0.001$) and the evening meal (8.6 vs 9.6 mmol/L; $P < 0.005$) for type 1 diabetics. No significant difference was noted in the noon meal.</p> <p>PPG was significantly lower with insulin lispro compared to REG in the morning meal only in type 2 diabetics (9.5 vs 10.4 mmol/L; $P < 0.001$).</p> <p>There was no significant difference in hypoglycemic events between the two treatment groups ($P = 0.677$ for type 1 diabetics and $P = 0.419$ for type 2 diabetics).</p> <p>Endpoint insulin dose was significantly higher with insulin lispro compared to regular human insulin in type 1 diabetics albeit the difference was small (0.63 vs 0.60 U/kg; $P = 0.015$). There were no significant differences in insulin doses in type 2 diabetics.</p> <p>Secondary: Not reported</p>
<p>Anderson et al.⁶⁰ (1997)</p> <p>Insulin lispro before meals and basal insulin</p> <p>vs</p> <p>regular insulin before meals and basal insulin</p>	<p>MC, OL, RCT</p> <p>Patients with type 1 diabetes and type 2 diabetes previously treated with REG, baseline HbA_{1c} 8.2% for both groups in patients with type 1 diabetes and baseline HbA_{1c}</p>	<p>N=631</p> <p>12 months</p>	<p>Primary: Effect on HbA_{1c}, postprandial rise in serum glucose, frequency of hypoglycemia, and insulin dose</p> <p>Secondary: Not reported</p>	<p>Primary: HbA_{1c} was significantly lower with insulin lispro compared to REG in type 1 diabetics (8.1 vs 8.3%; $P < 0.05$). There was no difference in HbA_{1c} between treatment groups for type 2 diabetics.</p> <p>Postprandial (two-hour) serum glucose rise was significantly reduced with insulin lispro compared to REG in type 1 diabetics (64%; $P = 0.007$) and type 2 diabetics (48%; $P = 0.004$).</p> <p>There was no difference in rates of hypoglycemia between the two treatment groups.</p> <p>There was a small, but significant reduction in premeal insulin dose in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	8.9% for REG and 8.7% for insulin aspart			<p>insulin lispro group (-0.03 U/kg; P=0.004) but a small and significant increase in the basal insulin dose (0.05 U/kg; P<0.001) in type 1 diabetics. There were no dose changes in the REG group.</p> <p>For type 2 diabetics, the daily dose increase of insulin was comparable between the treatment groups.</p> <p>Secondary: Not reported</p>
<p>Plank et al.⁶¹ (2005)</p> <p>Short-acting insulin analogs (insulin lispro and/or insulin aspart)</p> <p>vs</p> <p>regular insulin</p>	<p>MA</p> <p>Analysis of 42 randomized trials that compared short-acting insulin analogs vs REG in the treatment of type 1 diabetes and type 2 diabetes patients</p>	<p>N=7,933</p> <p>Duration varied</p>	<p>Primary: Effect on HbA_{1c} and number of hypoglycemic episodes</p> <p>Secondary: Quality of life, pregnancy outcomes, and adverse events</p>	<p>Primary: A small but significant difference in HbA_{1c} was observed with short-acting insulin analogs compared to REG in type 1 diabetes (-0.12%; 95% CI, -0.17 to -0.07).</p> <p>No significant differences in HbA_{1c} were observed with short-acting insulin analogs compared to REG in patients with type 2 diabetes (-0.02%; 95% CI, -0.10 to 0.07).</p> <p>No significant differences in hypoglycemic rates were observed with short-acting insulin analogs compared to REG in type 1 diabetic patients (-0.05 episodes/patient/month; 95% CI, -0.22 to 0.11).</p> <p>No significant differences in hypoglycemic rates were observed with short-acting insulin analogs compared to REG in patients with type 2 diabetes (-0.04 episodes/patient/month; 95% CI, -0.12 to 0.04).</p> <p>Secondary: Quality of life reported in type 1 diabetes favored short-acting insulin analogs in four studies and found no difference in three studies. No significant difference in quality of life was reported in studies with type 2 diabetics (two studies total).</p> <p>There were no significant differences in maternal or fetal outcomes between the two insulin groups.</p> <p>Comparable incidence and type of adverse events were reported for both insulin groups.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Siebenhofer et al.⁶² (2006)</p> <p>Rapid-acting insulin analogs (insulin lispro, insulin aspart, insulin glulisine)</p> <p>vs</p> <p>regular insulin</p>	<p>MA</p> <p>Analysis of 49 randomized trials that compared rapid-acting insulin analogs to REG in patients with type 1 diabetes and type 2 diabetes</p>	<p>N=8,274</p> <p>Duration varied</p>	<p>Primary: HbA_{1c}, hypoglycemia</p> <p>Secondary: Adverse events</p>	<p>Primary:</p> <p>In patients with type 1 diabetes, the WMD in HbA_{1c} was estimated to be -0.1% (95% CI, -0.2 to -0.1; P=0.01) in favor of insulin analogs compared to REG. In the subgroup analyses, results were divided into patients taking continuous SC insulin injections and patients taking conventional intensified insulin therapy. In patients taking continuous SC insulin therapy compared to REG, the WMD in HbA_{1c} was -0.2 (95% CI, -0.3 to -0.1; P value not reported) and in patients taking intensified insulin therapy compared to REG, the WMD was -0.1% (95% CI, -0.1 to 0.0; P value not reported).</p> <p>In patients with type 2 diabetes, the WMD of HbA_{1c} was estimated to be 0.0% (95% CI, -0.1 to 0.0). None of the studies evaluating differences in HbA_{1c} between insulin analogs and REG showed significant differences (P values not reported).</p> <p>In children, adolescents, pregnant patients with type 1 diabetes, there were no significant reductions in HbA_{1c} (P values were not reported).</p> <p>The WMD in overall hypoglycemia in patients with type 1 diabetes was -0.2 (95% CI, -1.1 to 0.7; P value not reported) for insulin analogs compared to REG. In patients with type 2 diabetes, the WMD was -0.2 (95% CI, -0.5 to 0.1; P=0.8). There were also no significant differences in overall hypoglycemia in pre-pubertal children. There were no statistically significant differences in these three groups. However, in the event rate of overall hypoglycemia in adolescents per patient per 30 days was significantly reduced with insulin analogs compared to REG (P=0.02). The event rate in pregnant women was significantly higher with insulin analogs compared to REG (P<0.05).</p> <p>Secondary:</p> <p>Overall, frequency and type of adverse events were comparable for the two treatment groups (P values not reported).</p>
<p>Intermediate-Acting and Long-Acting Insulins: Type 1 Diabetes Mellitus</p>				
<p>Thalange et al.⁶³ (2015)</p>	<p>MC, NI, OL, PG, RCT</p>	<p>N=350</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c} after 26 weeks</p>	<p>Primary: Non-inferiority of IDeg to IDet with respect to change in HbA_{1c} from baseline to week 26 was confirmed (estimated treatment difference, IDeg-</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin degludec (IDeg) once-daily vs insulin detemir (IDet) once- or twice-daily both with prandial insulin aspart</p>	<p>Children 1 to 17 years of age with type 1 diabetes who had been receiving insulin treatment (any regimen) for at least three months, without concomitant oral anti-diabetic drugs and with HbA_{1c} levels of ≤11%</p>	<p>(followed by 26-week extension; n=280)</p>	<p>Secondary: FPG, safety</p>	<p>IDet: 0.15%-points; 95% CI, -0.03 to 0.32). Secondary: At 52 weeks, HbA_{1c} was 7.9% (IDeg) vs 7.8% (IDet), change in mean FPG was -1.29 mmol/L (IDeg) vs 1.10 mmol/L (IDet) (estimated treatment difference, -1.62 mmol/L; P=0.0090), and mean basal insulin dose was 0.38 U/kg (IDeg) vs 0.55 U/kg (IDet). The majority of IDet treated patients (64%) required twice-daily administration to achieve glycemic targets. Hypoglycemia rates did not differ significantly between IDeg and IDet, but confirmed and severe hypoglycemia rates were numerically higher with IDeg (not significant) although nocturnal hypoglycemia rates were numerically lower (not significant). Rates of hyperglycemia with ketosis were significantly lower for IDeg vs IDet (0.7 vs 1.1 patient-years of exposure; P=0.0066). Both treatments were well tolerated with comparable rates of adverse events.</p>
<p>Davies et al.⁶⁴ (2015) Insulin degludec (IDeg) vs insulin detemir (IDet) both with prandial insulin aspart</p>	<p>ES, OL, PG, RCT Patients with type 1 diabetes mellitus currently treated with any basal-bolus insulin regimen for ≥12 months prior to screening and with HbA_{1c} ≤ 10.0% and BMI ≤35.0 kg/m²</p>	<p>N=370 1 year</p>	<p>Primary: Adverse events, hypoglycaemia, immunogenicity, insulin dose and body weight Secondary: Not reported</p>	<p>Primary: After one year, IDeg provided a 33% lower rate of nocturnal hypoglycaemia compared with IDet (estimated rate ratio [IDeg : IDet] 0.67; 95% CI, 0.51 to 0.88; P<0.05). IDeg improved HbA_{1c} after one year of treatment, similarly to IDet, but IDeg also provided a significantly greater reduction in fasting plasma glucose compared with IDet (estimated difference [IDeg - IDet], -1.11 mmol/l; 95% CI, -1.83 to -0.40; P<0.05). The rate of severe adverse events was 23 and 35 events per 100 patient-years of exposure in the IDeg and IDet treatment groups, respectively. Immunogenicity of IDeg, assayed by IDeg-specific antibodies and antibodies cross-reacting between IDeg and human insulin, was low throughout treatment. Body weight increased from baseline in both treatment arms, but the increase was greater in the IDeg compared with the IDet treatment arm (estimated difference, 1.07 kg; 95% CI, 0.47 to 1.67; P<0.05). Secondary: Not reported</p>
<p>Heller et al.⁶⁵ (2012) BEGIN: Basal-Bolus Type 1</p>	<p>MC, NI, OL, PG, RCT Patients ≥18 years of</p>	<p>N=629 52 weeks</p>	<p>Primary: Reduction in HbA_{1c} from base line at week 52</p>	<p>Primary: After 52 weeks of treatment, HbA_{1c} was reduced by 0.40% (SE 0.03) in the insulin degludec group and 0.39% (SE 0.07) in the insulin glargine group, with an ETD of -0.01% (95% CI, -0.14 to 0.11; P<0.0001), thus</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>study</p> <p>Insulin degludec QD (FlexPen[®]) plus insulin aspart with meals</p> <p>vs</p> <p>Insulin glargine QD (SoloStar[®]) plus insulin aspart with meals</p>	<p>age with type 1 diabetes for at least one year with at least one year of prior basal-bolus insulin therapy, HbA_{1c} ≤10%, BMI ≤35 kg/m²</p>		<p>Secondary:</p> <p>Proportion of patients that achieved HbA_{1c} <7%, overall rate of hypoglycemia, rate of nocturnal hypoglycemia (week 16 to end)</p>	<p>showing non-inferiority of insulin degludec compared to basal-bolus therapy with insulin glargine plus insulin aspart.</p> <p>Secondary:</p> <p>There was no significant difference in the proportion of participants that achieved a target HbA_{1c} of <7% (40% and 43% for the degludec and glargine groups respectively; P=0.48).</p> <p>The number of confirmed episodes of hypoglycemia were similar in both the insulin degludec and insulin glargine groups (42.54 and 40.18 episodes per patient-year exposure, respectively) with a rate ratio of 1.07 (95% CI, 0.89 to 1.28; P=0.48).</p> <p>The number of confirmed episodes of nocturnal hypoglycemia from week 16 to 52 was significantly reduced in the insulin degludec group compared with the insulin glargine group (3.91 compared with 5.22 episodes per patient-year exposure, respectively) with a rate ratio of 0.73 (95% CI, 0.56 to 0.96; P=0.024).</p>
<p>Bode et al.⁶⁶ (2013) BEGIN: Basal-Bolus Type 1 study</p> <p>Insulin degludec QD (FlexPen[®]) plus insulin aspart with meals</p> <p>vs</p> <p>Insulin glargine QD (SoloStar[®]) plus insulin aspart with meals</p>	<p>ES of a MC, NI, OL, PG, RCT (Heller et al)</p> <p>Patients ≥18 years of age with type 1 diabetes for at least one year with at least one year of prior basal-bolus insulin therapy, HbA_{1c} ≤10%, BMI ≤35 kg/m²</p>	<p>N=629</p> <p>104 weeks</p>	<p>Primary:</p> <p>Reduction in HbA_{1c} from baseline at week 104</p> <p>Secondary:</p> <p>Overall rate of hypoglycemia, rate of nocturnal hypoglycemia</p>	<p>Primary:</p> <p>After 104 weeks, the observed mean HbA_{1c} was reduced by 0.27%-points and 0.24% (full analysis set) and by 0.31% and 0.24% (extension trial set) with insulin degludec and insulin glargine, respectively. ETD was -0.04% (full analysis set) was not statistically significant (95% CI, -0.17 to 0.09, P value not reported)</p> <p>Secondary:</p> <p>The rate of overall hypoglycemia was similar in both groups (P value not reported).</p> <p>The rate of nocturnal hypoglycemia was significantly lower with insulin degludec compared with insulin glargine (3.9 compared with 5.3 episodes per patient-year of exposure, respectively) with an estimated rate ratio of 0.75 (95% CI, 0.59 to 0.95; P=0.02).</p>
<p>Mathieu et al.⁶⁷</p>	<p>MC, NI, OL, PG,</p>	<p>N=493</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2013) BEGIN: Flex Type 1 study</p> <p>Insulin degludec (FlexPen®) QD (forced-flex dosing) + insulin aspart with meals</p> <p>vs</p> <p>Insulin degludec (FlexPen®) QD (same-time dosing) + insulin aspart with meals</p> <p>vs</p> <p>Insulin glargine (SoloStar®) QD (same-time dosing) plus insulin aspart with meals</p>	<p>RCT</p> <p>Patients ≥18 years of age with type 1 diabetes current basal-bolus insulin therapy, HbA_{1c} ≤10%, BMI ≤35 kg/m²</p>	<p>26 weeks</p>	<p>Change in HbA_{1c} from baseline to week 26</p> <p>Secondary: FPG and SMPG profiles, overall hypoglycemia, nocturnal hypoglycemia</p>	<p>The mean decrease from baseline in HbA_{1c} was -0.40% in the degludec (forced-flex) group, -0.41% in the degludec (same-time) group, and -0.58% in the glargine (same-time) group. The ETD between the degludec (forced-flex) group and the glargine (same-time) group was 0.17% (95% CI, 0.04 to 0.30; no P value reported). ETD between the two degludec groups (forced-flex vs same-time) was 0.01% (95% CI, -0.13 to 0.14). The ETD between the degludec (same-time) and glargine (same-time) groups was not reported.</p> <p>Secondary: Laboratory-measured FPG decreased from baseline to week 26 by -1.28, -2.54, and -1.33 mmol/L in the degludec (forced-flex), degludec (same-time) and glargine (same time) groups, respectively. There was no significant difference in FPG when degludec (forced-flex) was compared with glargine (no P value reported). However, there was a significant difference in FPG in favor of degludec (same-time) when compared to degludec (forced-flex) with an ETD of 0.95 mmol/L (95% CI, 0.15 to 1.75; P=0.021).</p> <p>After 26 weeks, observed 9-point SMPG means appeared similar among groups. There was a significant difference in favor of insulin degludec (forced-flex) compared with the glargine group only at the “before lunch” time. The ETD was 0.85 mmol/L (95% CI, 0.12 to 1.57; P=0.022). The proportion of participants who attained prebreakfast SMPG target less than 5.0 mmol/L at week 26 was 11.3% (degludec forced-flex), 23.8% (degludec same-time), and 18.4% (glargine same-time).</p> <p>Overall, confirmed and severe hypoglycemia rates were similar across groups at week 26 (no P values reported). There rates of nocturnal hypoglycemia were generally lower with insulin degludec forced-flex dosing (no P value reported).</p>
<p>Pieber et al.⁶⁸ (2007)</p> <p>Insulin detemir BID (AM and HS) and insulin</p>	<p>OL, PG, RCT</p> <p>Men and women ≥18 years of age with type 1 diabetes for at</p>	<p>N=322</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c}, change in FPG, hypoglycemia</p>	<p>Primary: At 26 weeks, both groups had comparable changes in HbA_{1c} (between-treatment difference, -0.03; 95% CI, -0.25 to 0.19; P value not reported).</p> <p>However, insulin glargine resulted in significantly lower home measured FPG than insulin detemir (7.0 vs 7.7 mmol/L, respectively; P<0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>aspart before meals</p> <p>vs</p> <p>insulin glargine at bedtime and insulin aspart before meals</p> <p>Insulin doses were titrated to achieve a target of ≤ 7.3 mmol/L for pre-breakfast and pre-evening meal plasma glucose for insulin detemir and pre-breakfast plasma glucose for insulin glargine.</p>	<p>least 1 year who had a BMI ≤ 35 kg/m² and HbA_{1c} 7.5 to 12.0%</p>		<p>Secondary: Not reported</p>	<p>The overall risk of hypoglycemia was comparable in both treatment groups (RR, 0.96; 95% CI, 0.68 to 1.35; P=0.811). However, insulin detemir resulted in lower rates of nocturnal hypoglycemia (episodes/subject-year) than with insulin glargine (4.3 vs 6.6, respectively; P<0.05).</p> <p>Secondary: Not reported</p>
<p>Heller et al.⁶⁹ (2009)</p> <p>Insulin detemir PM or BID (AM and PM) and insulin aspart before meals</p> <p>vs</p> <p>insulin glargine PM and insulin aspart before meals</p> <p>Basal insulin doses</p>	<p>MC, NI, OL, PG, RCT</p> <p>Patients ≥ 18 years of age with type 1 diabetes for ≥ 1 year who were receiving basal-bolus insulin regimen for ≥ 3 months with HbA_{1c} $\leq 11.0\%$</p>	<p>N=443</p> <p>52 weeks</p>	<p>Primary: HbA_{1c} at 52 weeks</p> <p>Secondary: Proportion of patients achieving HbA_{1c} $\leq 7.0\%$ with or without major hypoglycemia in the last month of treatment, FPG, within-patient variation in self-monitored pre-</p>	<p>Primary: Change in HbA_{1c} from baseline at 52 weeks was -0.53 and -0.54% with insulin detemir and insulin glargine, respectively (mean difference, 0.01%; 95% CI, -0.13 to 0.16), confirming non-inferiority.</p> <p>Patients receiving twice-daily insulin detemir experienced greater HbA_{1c} reduction (-0.58%) compared to those receiving once-daily insulin detemir (-0.49%; P value not reported).</p> <p>Secondary: Similar percentage of patients achieved HbA_{1c} $\leq 7.0\%$ with insulin detemir compared to insulin glargine (33.0 vs 30.4%; P value not significant). The HbA_{1c} goal was achieved without major hypoglycemia during the last month of treatment in 31.9 and 28.9% of patients in the insulin detemir and insulin glargine groups, respectively (P value NS).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>were titrated to achieve PG \leq108 mg/dL.</p> <p>Prandial insulin doses were titrated to achieve PPG \leq162 mg/dL.</p>			<p>breakfast and pre-dinner blood glucose, 10-point self-monitored plasma glucose profiles and safety</p>	<p>No significant differences were observed between the two groups with regard to changes in FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose and 10-point self-monitored plasma glucose profiles.</p> <p>During the study, 91.6% of patients in the insulin detemir group and 88.2% in the insulin glargine group met the criteria to switch from once- to twice-daily dosing. At the end of the study, 65.8 and 4.8% of patients in the insulin detemir and insulin glargine groups, respectively, were receiving BID dosing. The total basal insulin dose at the end of the study was 0.40 units/kg and 0.33 units/kg with insulin detemir and insulin glargine, respectively.</p> <p>There were no significant differences between the two groups with regard to weight gain and incidence of hypoglycemia. Adverse events were reported in 92.6 and 89.6% of patients in the insulin detemir and insulin glargine groups, respectively. Twelve and one serious adverse events were probably or possibly related to insulin detemir and insulin glargine, respectively. Injection site reactions were reported more frequently with insulin detemir compared to insulin glargine (8.0 vs 1.4%; P value not reported).</p>
<p>Vague et al.⁷⁰ (2003)</p> <p>Insulin detemir BID and insulin aspart before meals</p> <p>vs</p> <p>NPH insulin BID and insulin aspart before meals</p> <p>Basal insulin</p>	<p>MC, OL, PG, RCT</p> <p>Adult type 1 diabetes patients on a basal-bolus insulin regimen for \geq2 months; baseline HbA_{1c} 8.18% for participants in the insulin detemir group and 8.11% for those randomized into the NPH group</p>	<p>N=448</p> <p>26 weeks</p>	<p>Primary: Effect on HbA_{1c}, FPG, variability in fasting self monitoring of blood glucose, weight gain, and frequency of hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: After six months, both insulin detemir and NPH reduced HbA_{1c} -0.55% (P value NS).</p> <p>After six months, FPG with insulin detemir (9.19 mmol/L) was comparable to NPH (9.94 mmol/L; P=0.097).</p> <p>There was significantly less day-to-day fluctuation of fasting self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P<0.001).</p> <p>Body weight change from baseline was significantly lower with insulin detemir (-0.2 kg) compared to NPH (0.7 kg; P<0.001).</p> <p>The RR of hypoglycemia was 22% lower with insulin detemir compared</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL.</p>				<p>to NPH (P<0.05). The RR of nocturnal hypoglycemia was 34% lower with insulin detemir compared to NPH (P<0.005).</p> <p>Secondary: Not reported</p>
<p>Hermansen et al.⁷¹ (2004)</p> <p>Insulin detemir BID and insulin aspart before meals</p> <p>vs</p> <p>NPH insulin BID and insulin aspart before meals</p>	<p>OL, RCT</p> <p>Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥6 months, baseline HbA_{1c} 8.48% for participants in the insulin detemir group and 8.29% for those randomized into the NPH group</p>	<p>N=595</p> <p>18 weeks</p>	<p>Primary: Effect on HbA_{1c}, FPG, self monitoring of blood glucose profile, weight gain, and frequency of hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: After 18 weeks, HbA_{1c} was significantly lower in the insulin detemir group (7.88%) compared to the NPH group (8.11%; P<0.001).</p> <p>After 18 weeks, there was no significant difference in FPG with insulin detemir (7.58 mmol/L) compared to NPH (8.10 mmol/L; P>0.05).</p> <p>There was significantly less day-to-day fluctuation of self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P<0.05).</p> <p>Body weight change from baseline was significantly lower with insulin detemir (-0.95 kg) compared to NPH (0.07 kg; P<0.001).</p> <p>The risk of hypoglycemia was 21% lower with insulin detemir compared to NPH (P=0.036). The risk of nocturnal hypoglycemia was 55% lower with insulin detemir compared to NPH (P<0.001).</p> <p>Secondary: Not reported</p>
<p>Home et al.⁷² (2004)</p> <p>Insulin detemir every morning (QAM) and at bedtime plus premeal insulin aspart</p> <p>vs</p>	<p>MC, OL, PG, RCT</p> <p>Men and women >18 years of age with type 1 diabetes for >1 year already on mealtime plus basal insulin for >2 months, with a basal dose <100 IU/day, HbA_{1c}</p>	<p>N=409</p> <p>16 weeks</p>	<p>Primary: Change in HbA_{1c}, change in FPG from baseline</p> <p>Secondary: 10-point self monitoring of blood glucose, frequency of hypoglycemia,</p>	<p>Primary: At 16 weeks, there was no significant difference in HbA_{1c} between all treatment groups (P=0.082). Insulin detemir every 12 hours had a reduction in HbA_{1c} of -0.85%. When dosed every morning and at bedtime, HbA_{1c} was reduced by -0.82%, whereas, NPH only reduced HbA_{1c} by -0.65%. In combination, both detemir groups resulted in significantly greater reductions in HbA_{1c} than NPH (difference, -0.18%; 95% CI, -0.34 to -0.02; P=0.027).</p> <p>FPG levels were statistically significantly lower in both the detemir every 12 hours (P=0.004) and detemir every morning and at bedtime group (P<0.001) than the NPH group. Differences between the detemir groups</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>insulin detemir every 12 hours (Q12H) plus premeal insulin aspart</p> <p>vs</p> <p>NPH insulin BID plus premeal insulin aspart</p> <p>Doses were titrated to achieve target FPG goals 4.0 to 7.0 mmol/L and PPG goals ≤ 10 mmol/L.</p>	<p>$\leq 12.0\%$, BMI ≤ 35.5 kg/m²</p>		<p>weight gain</p>	<p>did not result in statistical significance.</p> <p>Secondary: Overall 10-point self monitoring of blood glucose profiles were comparable between the three treatment groups ($P > 0.05$).</p> <p>The overall risk of hypoglycemia was significantly lower with insulin detemir every 12 hours (25%; $P = 0.046$) and insulin detemir every morning and at bedtime (32%; $P = 0.002$) compared to NPH. There were no significant differences in risk of nocturnal hypoglycemia between insulin detemir every 12 hours and NPH. However, when dosed every morning and at bedtime, insulin detemir had a significantly lower risk of nocturnal hypoglycemia than NPH (53%; $P < 0.001$).</p> <p>Mean weight change was significantly decreased with insulin detemir every 12 hours (-0.8 kg; $P = 0.006$) and insulin detemir every morning and at bedtime (-0.6 kg; $P = 0.040$) when compared to NPH. However, there was no significant difference in weight change between the insulin detemir groups ($P > 0.05$).</p>
<p>Russell-Jones et al.⁷³ (2004)</p> <p>Insulin detemir HS and regular insulin before meals</p> <p>vs</p> <p>NPH insulin HS and regular insulin before meals</p> <p>Doses were titrated to achieve</p>	<p>MC, OL, PG, RCT</p> <p>Men and women ≥ 18 years of age with type 1 diabetes for ≥ 1 year already on basal or premixed insulin QD in the evening (5 PM to 11 PM) and REG before meals for ≥ 2 months and $HbA_{1c} \leq 12.0\%$</p>	<p>N=749</p> <p>6 months</p>	<p>Primary: Change in HbA_{1c} from baseline, change in FPG and fasting self monitoring of blood glucose, nine-point self monitoring of blood glucose profile, 24-hour continuous blood glucose monitoring, hypoglycemia, body weight</p> <p>Secondary:</p>	<p>Primary: Mean HbA_{1c} value decreased by -0.06% with insulin detemir while HbA_{1c} increased by 0.06% with NPH. However, the baseline-adjusted mean HbA_{1c} values did not significantly differ between groups (-0.12%; 95% CI, -0.25 to 0.02; $P = 0.083$).</p> <p>Both FPG and fasting self monitoring of blood glucose decreased similarly in the insulin detemir group and were slightly decreased with NPH. Both endpoints resulted in significant reductions with insulin detemir in comparison to NPH ($P = 0.001$ and $P < 0.001$, respectively).</p> <p>Nine-point self monitoring of blood glucose profiles demonstrated significantly lower glucose values before breakfast with insulin detemir when compared to NPH ($P < 0.001$).</p> <p>In study participants that underwent 24-hour continuous blood glucose monitoring, insulin detemir had significantly less blood glucose fluctuations for mean levels nocturnally and over 24 hours ($P < 0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>target FPG goal 72 to 126 mg/dL and PPG goal of 180 mg/dL.</p>			<p>Not reported</p>	<p>Overall rates of hypoglycemia were comparable between groups. However, the RR of nocturnal hypoglycemia was 26% lower with insulin detemir compared to NPH (P=0.003). There was also a 30% risk reduction of minor hypoglycemic episodes during the night with insulin detemir (P=0.003).</p> <p>Body weight gain was significantly lower with insulin detemir compared to NPH (-0.54 kg; P=0.024).</p> <p>Secondary: Not reported</p>
<p>Standl et al.⁷⁴ (2004)</p> <p>Insulin detemir BID and regular insulin before meals</p> <p>vs</p> <p>NPH insulin BID and regular insulin before meals</p> <p>Basal insulin doses were adjusted to achieve FPG 4.0 to 7.0 mmol/L (72 to 126 mg/dL) and PPG <10 mmol/L (180 mg/dL).</p>	<p>ES, MC, OL, PG, RCT</p> <p>Adult patients with type 1 diabetes on a basal-bolus insulin regimen for ≥2 months, baseline HbA_{1c} 7.72% for participants taking insulin detemir and 7.66% for those randomized into the NPH group</p>	<p>N=421 (n=289 in the 6 month extension trial)</p> <p>12 months (6-month treatment period and 6-month extension trial)</p>	<p>Primary: Effect on HbA_{1c}, FPG, nine-point self monitoring of blood glucose profile, weight gain, and frequency of hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: After 12 months, HbA_{1c} was comparable between the insulin detemir group (7.88%) and the NPH group (7.78%; P=0.288).</p> <p>After 12 months, there was no significant difference in FPG with insulin detemir (10.1 mmol/L) compared to NPH (9.84 mmol/L; P=0.665).</p> <p>Mean nine-point self monitoring of blood glucose profiles showed significantly lower blood glucose 90-minutes after lunch and dinner (P<0.05). There were no significant differences at other times in the profile.</p> <p>After 12 months, body weight change from baseline was significantly lower with insulin detemir (-1.44 kg) compared to NPH (0.3 kg; P<0.001).</p> <p>There was no significant difference in the overall risk of hypoglycemia between insulin detemir and NPH (P=0.139). There was no significant difference in the risk of nocturnal hypoglycemia between insulin detemir and NPH (P=0.067).</p> <p>Secondary: Not reported</p>
<p>De Leeuw et al.⁷⁵</p>	<p>ES, MC, OL, PG,</p>	<p>N=316</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2005)</p> <p>Insulin detemir BID and insulin aspart before meals</p> <p>vs</p> <p>NPH insulin BID and insulin aspart before meals</p> <p>Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL.</p>	<p>RCT</p> <p>Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥ 2 months, baseline HbA_{1c} 8.18% for participants in the insulin detemir group and 8.03% for those randomized into the NPH group</p>	<p>12 months (6-month treatment period and 6-month extension period)</p>	<p>Effect on HbA_{1c}, FPG, nine-point self monitoring of blood glucose, frequency of hypoglycemia, and weight gain</p> <p>Secondary: Not reported</p>	<p>Similar reductions in mean HbA_{1c} values were observed in both treatment groups. After 12 months, insulin detemir reduced HbA_{1c} -0.64% and NPH reduced HbA_{1c} -0.56% (P value was not reported).</p> <p>After 12 months, FPG with insulin detemir (10.7 mmol/L) was comparable to NPH (10.8 mmol/L; P value not reported).</p> <p>Nine-point self monitoring of blood glucose profiles were comparable between insulin detemir when compared to NPH (value not reported; P<0.24).</p> <p>There were no significant differences in overall rates of hypoglycemia between treatment groups. The RR of nocturnal hypoglycemia was 32% lower with insulin detemir when compared to NPH (P=0.016).</p> <p>After 12 months, body weight gain was significantly lower with insulin detemir compared to NPH (-1.34 kg; P<0.001).</p> <p>Secondary: Not reported</p>
<p>Pieber et al.⁷⁶ (2005)</p> <p>Insulin detemir BID (AM and PM) and insulin aspart before meals</p> <p>vs</p> <p>insulin detemir BID (AM and HS) and insulin aspart before meals</p>	<p>MC, OL, PG, RCT</p> <p>Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥ 2 months; baseline HbA_{1c} 8.01% for participants taking insulin detemir every morning and at dinner, 8.13% for those taking insulin detemir every morning and at bedtime, and</p>	<p>N=400</p> <p>16 weeks</p>	<p>Primary: Effect on HbA_{1c} and FPG</p> <p>Secondary: Variability in fasting self monitoring of blood glucose, 10-point self monitoring of blood glucose, 24-hour glucose profile, frequency of hypoglycemia, and weight gain</p>	<p>Primary: HbA_{1c} was significantly reduced in all three groups. Insulin detemir dosed in the morning and at dinner reduced HbA_{1c} -0.43%. When dosed in the morning and at bedtime, HbA_{1c} was reduced -0.49%. NPH reduced HbA_{1c} -0.39%. There was no significant difference between the groups (P=0.64).</p> <p>FPG reductions were significantly greater with insulin detemir dosed in the morning and dinner (-0.17 mmol/L; P<0.001) and insulin detemir dosed in the morning and bedtime (-1.48 mmol/L; P<0.006) when compared to NPH (0.49 mmol/L). There was no significant difference in FPG between the insulin detemir groups (P=0.15).</p> <p>Secondary: Within-person variation in fasting self monitoring of blood glucose was significantly lower with either insulin detemir treatments compared to NPH (P<0.001). There was no significant difference in fasting self</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>NPH insulin BID (AM and HS) and insulin aspart before meals</p> <p>Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL.</p>	<p>8.08% for those randomized into the NPH group</p>			<p>monitoring of blood glucose between the insulin detemir groups (P=0.48).</p> <p>Overall 10-point self monitoring of blood glucose profiles were comparable between the three groups (P=0.103).</p> <p>Twenty four-hour glucose profiles demonstrated lower glucose fluctuations with both insulin detemir treatments compared to NPH (P=0.049).</p> <p>Overall and nocturnal rates of hypoglycemia were comparable between all groups.</p> <p>Mean weight changes were significantly different with detemir dosed in the morning and dinner (-0.6 kg; P<0.001) and insulin detemir dosed in the morning and bedtime (0.1 kg; P=0.050) when compared to NPH (0.7 kg).</p>
<p>Køglendørf et al.⁷⁷ (2006)</p> <p>Insulin detemir BID and insulin aspart before meals for 16 weeks</p> <p>vs</p> <p>NPH insulin BID and insulin aspart before meals for 16 weeks</p>	<p>OL, RCT, XO</p> <p>Adult type 1 diabetes patients on a basal-bolus insulin regimen for >4 months, baseline HbA_{1c} 7.9% for participants receiving insulin detemir first and 7.9% for those receiving NPH first</p>	<p>N=130</p> <p>32 weeks</p>	<p>Primary: Incidence of self-recorded hypoglycemia</p> <p>Secondary: Incidence of severe hypoglycemic episodes, effect on HbA_{1c} and self monitoring plasma glucose</p>	<p>Primary: The RR of hypoglycemia was 18% lower with insulin detemir compared to NPH (P=0.001). The RR of nocturnal hypoglycemia was 50% lower with insulin detemir compared to NPH (P<0.0001).</p> <p>Secondary: There were 19 severe hypoglycemic episodes with insulin detemir and 33 episodes with NPH; however, due to the low number of episodes an analysis could not be conducted.</p> <p>HbA_{1c} was reduced by approximately -0.3% in both treatment arms (P value was not reported).</p> <p>There was significantly less day-to-day fluctuation of self-monitored plasma glucose profiles with insulin detemir when compared to NPH (P<0.001).</p>
<p>Robertson et al.⁷⁸ (2007)</p> <p>Insulin detemir</p>	<p>OL, PG, RCT</p> <p>Children 6 to 17 years of age with</p>	<p>N=347</p> <p>26 weeks</p>	<p>Primary: HbA_{1c} and eight-point plasma glucose profiles</p>	<p>Primary: HbA_{1c} at 26 weeks decreased by approximately -0.8% in both the insulin detemir and NPH groups (8.0 vs 7.9%, respectively; 95% CI, -0.1 to 0.3; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>HS or BID (AM and HS) and insulin aspart before meals</p> <p>vs</p> <p>NPH insulin QD or BID and insulin aspart before meals</p> <p>Insulin aspart doses were titrated to achieve PPG 121 to 182 mg/dL.</p>	<p>type 1 diabetes, treated with insulin for at least 12 months (total daily dose ≤ 2 U/kg), and HbA_{1c} $\leq 12.0\%$</p>		<p>assessed at 18 and 26 weeks, self-measured FPG on four days after 18 and 26 weeks</p> <p>Secondary: Hypoglycemia</p>	<p>The mean eight-point plasma glucose profiles after 26 weeks were assumed parallel and did not have a statistically significant difference between insulin detemir and NPH (P=0.302). Plasma glucose levels were lower with insulin detemir than NPH at all time points except at 03.00 hour. However, the analysis of self-measured nocturnal plasma glucose at 03.00 hour did not show a statistical difference between treatments (P=0.194).</p> <p>Mean self-measured FPG after 26 weeks was lower with insulin detemir than with NPH (P=0.022). Within-subject FPG variation also showed lower FPG levels with insulin detemir than NPH (P<0.001).</p> <p>Secondary: The study determined that the risk of having nocturnal hypoglycemia was 26% lower with insulin detemir (P=0.041). However, the risks of 24-hour and diurnal hypoglycemia were similar in both groups (P=0.351 and P=0.492, respectively). Also, the risks of having severe episodes, confirmed episodes or symptoms of hypoglycemia were similar in both groups (P=0.799, P=0.275, and P=0.425, respectively).</p>
<p>Bartley et al.⁷⁹ (2008)</p> <p>Insulin detemir PM or BID and insulin aspart before meals</p> <p>vs</p> <p>NPH insulin PM or BID and insulin aspart before meals</p> <p>Insulin doses were titrated to achieve plasma glucose target ≤ 6.0 mmol/l</p>	<p>OL, PG, RCT</p> <p>Patients ≥ 18 years of age with type 1 diabetes, HbA_{1c} $\leq 11.0\%$, BMI ≤ 35.0 kg/m², and receiving a basal-bolus insulin regimen ≥ 3 months</p>	<p>N=497</p> <p>24 months</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, proportion of patients achieving HbA_{1c} $\leq 7.0\%$ without hypoglycemia, incidence in hypoglycemia, change in baseline body weight, safety</p>	<p>Primary: Insulin detemir resulted in significantly greater decreases in HbA_{1c} compared to NPH (final HbA_{1c}, 7.36 vs 7.50%; decrease, -0.94 vs -0.72%; difference, -0.22%; 95% CI, -0.41 to -0.03).</p> <p>Secondary: Insulin detemir significantly decreased FPG compared to NPH (final FPG, 8.35 vs 9.43 mmol/L; P=0.019).</p> <p>Significantly more patients receiving insulin detemir achieved HbA_{1c} $\leq 7.0\%$ without hypoglycemia compared to patients receiving NPH (22 vs 13%; P=0.019).</p> <p>The risk of major and nocturnal hypoglycemia was significantly lower with insulin detemir (P<0.001). Specifically, insulin detemir was associated with a 69 and 49% lower risk of major and nocturnal hypoglycemia.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
before breakfast and dinner.				<p>Insulin detemir resulted in significantly less weight gain compared to NPH (1.7 vs 2.7 kg; P=0.024).</p> <p>The overall safety profile was similar between the two treatments. Four deaths were reported with insulin detemir (cardiorespiratory arrest in relation to status epilepticus, sudden death, bronchopneumonia, and MI following surgery). All events were judged to not be related to insulin detemir. Withdrawals due to adverse events were more common with insulin detemir.</p>
<p>Ratner et al.⁸⁰ (2000)</p> <p>Insulin glargine HS</p> <p>vs</p> <p>NPH insulin HS or BID (AM and HS)</p> <p>Doses of both insulins were titrated to achieve preprandial blood glucose 4.4 to 6.7 mmol/L.</p>	<p>PG, RCT</p> <p>Type 1 diabetes patients, baseline HbA_{1c} 7.7% in both groups</p>	<p>N=534</p> <p>28 weeks</p>	<p>Primary: Effect on HbA_{1c}, FPG, and incidence of hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: Reduction in HbA_{1c} was similar with NPH (-0.21%) and insulin glargine (-0.16%; P=0.4408).</p> <p>Reduction in FPG was similar with NPH (-0.94 mmol/L) and insulin glargine (-1.12 mmol/L; P=0.3546).</p> <p>After the one month titration phase, significantly less patients on insulin glargine reported symptomatic hypoglycemia (39.9 vs 49.2%; P=0.0219) or nocturnal hypoglycemia (18.2 vs 27.1%; P=0.0116).</p> <p>Overall incidence of all symptomatic hypoglycemia was similar between treatment groups throughout the study.</p> <p>Secondary: Not reported</p>
<p>Tan et al.⁸¹ (2004)</p> <p>Analysis was on data 6 months prior to initiating insulin glargine therapy and data 6 months after initiating</p>	<p>RETRO</p> <p>Patients ≤18 years of age with type 1 diabetes when initiating insulin glargine therapy between June 1, 2001 and June 30,</p>	<p>N=71</p> <p>12 months</p>	<p>Primary: Change in HbA_{1c}, blood glucose concentrations, hypoglycemia (number of self-reported symptomatic hypoglycemia and</p>	<p>Primary: There was no difference in HbA_{1c} between baseline and six months after initiating insulin glargine therapy (8.9±1.6% and 8.9±1.5%, respectively). In the divided groups, there was no statistical difference in the change in HbA_{1c} between patients taking insulin glargine only vs patients taking insulin glargine plus NPH (P value not reported).</p> <p>Mean blood glucose concentrations decreased slightly after initiating insulin glargine in all subjects. Patients taking insulin glargine plus NPH</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>insulin glargine therapy.</p> <p>Patients were divided into those taking insulin glargine only and those taking insulin glargine plus NPH insulin in the AM.</p>	<p>2002, not using continuous SC insulin infusion or inhaled insulin before starting insulin glargine therapy</p>		<p>number of blood glucose readings <50 mg/dL)</p> <p>Secondary: Not reported</p>	<p>had slight improvements in average blood glucose levels, whereas patients taking insulin glargine only had a slight deterioration and a slight rise in average blood glucose levels. All changes were not statistically significant (P values not reported).</p> <p>There was a decrease in self-reported episodes of symptomatic hypoglycemia after initiating insulin glargine therapy. However, there was no difference between baseline and after starting insulin glargine therapy in the frequency of blood glucose values <50 mg/dL (P value not reported).</p> <p>Secondary: Not reported</p>
<p>Ashwell et al.⁸² (2006)</p> <p>Insulin glargine HS and insulin lispro before meals for 16 weeks</p> <p>vs</p> <p>NPH insulin QD or BID and regular insulin before meals for 16 weeks</p> <p>Doses were adjusted to achieve target pre-breakfast, preprandial, and postprandial levels of 4.0 to 6.5 mmol/L, in the absence of hypoglycemia.</p>	<p>MC, RCT, 2-way, XO</p> <p>Patients aged 18 to 65 years of age with type 1 diabetes, no previous experience with insulin glargine, previously on a multiple insulin injection regimen for at least 1 year, random C-peptide ≤0.10 nmol/L, HbA_{1c} 7.0 to 9.5%</p>	<p>N=56</p> <p>32 weeks</p>	<p>Primary: HbA_{1c} at treatment endpoints</p> <p>Secondary: Prebreakfast self monitoring of blood glucose concentration, 24-hour eight-point self monitoring of blood glucose levels, 24-hour inpatient plasma glucose levels, monthly rate of hypoglycemia</p>	<p>Primary: At 16 weeks, HbA_{1c} was lower with insulin glargine compared to NPH (between treatment difference, -0.5; 95% CI, -0.7 to -0.3; P<0.001).</p> <p>Secondary: Prebreakfast self monitoring of blood glucose concentration was lower in the insulin glargine group than the NPH group (between treatment difference, -1.5; 95% CI, -2.6 to -0.5; P<0.005).</p> <p>Self monitoring of blood glucose concentrations were lower before and after breakfast with insulin glargine compared to NPH. The 24-hour eight-point self monitoring of blood glucose concentrations was also lower with insulin glargine (between treatment difference, -1.9; 95% CI, -3.1 to -0.8; P=0.001).</p> <p>During the inpatient assessment, 24-hour eight-point self monitoring of blood glucose levels were lower at all points with insulin glargine compared to NPH (P=0.037 for plasma glucose AUC; P=0.002 for PPG AUC; P=0.038 for plasma glucose before breakfast).</p> <p>Seventy-two percent of patients taking insulin glargine reported nocturnal hypoglycemia compared to 83% of patients taking NPH. This resulted in a -44% reduction in the monthly rate of nocturnal hypoglycemia with insulin glargine compared to NPH (P<0.001).</p>
<p>Herwig et al.⁸³</p>	<p>OL</p>	<p>N=142</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2007)</p> <p>Insulin glargine QD and regular insulin or insulin lispro before meals</p> <p>vs</p> <p>NPH insulin QD to TID and regular insulin or insulin lispro before meals</p> <p>Doses of insulin glargine were titrated to achieve target FBG 4.4 to 7.8 mmol/L and doses of NPH insulin were titrated to achieve target FBG 4.4 to 8.9 mmol/L.</p>	<p>Pediatric patients with type 1 diabetes for >1 year duration</p>	<p>20±10 months</p>	<p>HbA_{1c}, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>HbA_{1c} significantly increased from 7.3±1.0% to 7.6±1.1% (P=0.003) and from 7.7±1.6% to 8.3±1.5% (P=0.0001) in both the insulin glargine and NPH groups.</p> <p>The incidence of symptomatic hypoglycemia was comparable between both groups; however, the overall incidence of severe hypoglycemia was significantly lower in the insulin glargine group (P=0.002).</p> <p>Secondary: Not reported</p>
<p>Kudva et al.⁸⁴ (2007)</p> <p>Insulin glargine and insulin aspart before meals</p> <p>vs</p> <p>ultralente insulin and insulin aspart before meals</p>	<p>RCT, XO</p> <p>Patients with median age of 43 years with type 1 diabetes</p>	<p>N=22</p> <p>16 weeks</p>	<p>Primary: Hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: Measures of glycemic variation did not differ significantly between insulin glargine and ultralente insulin. In the insulin glargine group, the standard deviation of blood glucose showed a tendency to be lower and the standard deviation of nocturnal blood glucose concentrations was significantly lower. However, glucose concentrations were significantly lower during the one hour before and three hours after lunch with ultralente insulin.</p> <p>Secondary: Not reported</p>
<p>Chatterjee et al.⁸⁵</p>	<p>OL, RCT, XO</p>	<p>N=60</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Insulin glargine QD and insulin aspart before meals for 16 weeks vs NPH insulin BID and insulin aspart before meals for 16 weeks	Patients 18 to 75 years of age with type 1 diabetes for at least 6 months on either BID or multiple dose insulin injections, BMI <45 kg/m ² , HbA _{1c} 6.0 to 11.0%	36 weeks	Change in HbA _{1c} Secondary: Frequency of overall hypoglycemic episodes, change in FPG, body weight, lipid profile	At 36 weeks, treatment with insulin glargine resulted in lower HbA _{1c} levels compared to NPH (between-treatment difference, -0.19±0.09; 95% CI, -0.36 to 0.01; P=0.04). At the end of the second treatment period, those patients switching from glargine to NPH experienced an increase in HbA _{1c} of 0.16%, whereas those who switched from NPH to glargine experienced a reduction of -0.1%. Secondary: Both groups had similar mean incidences of overall hypoglycemic episodes (between-treatment difference, 1.21; 95% CI, 0.56 to 2.64; P=0.63). The OR for the incidence of hypoglycemia compared in both groups was 1.2 (95% CI, 0.55 to 2.59; P value not reported). FPG was also lower with insulin glargine vs NPH (between-treatment difference, -3.00; 95% CI, -4.80 to -1.20; P<0.01). There was no significant difference in change in body weight between both groups (mean difference, -0.24; 95% CI, -0.87 to 0.39; P=0.45). Similarly, there was no difference in TC or TG levels between groups (P value not reported).
Manini et al. ⁸⁶ (2007) Insulin glargine vs intensive insulin treatment (NPH)	RCT Patients with a mean age of 46 years with type 1 diabetes for at least 1 year duration and suboptimal glucose control under intensive insulin treatment	N=47 8 months	Primary: Change in HbA _{1c} , health-related quality of life Secondary: Not reported	Primary: Insulin glargine resulted in a mean HbA _{1c} decrease of -0.7% from baseline (P<0.0001). Insulin glargine also resulted in improved health-related quality of life scores using a Well-being Enquiry for Diabetics questionnaire. The results showed improvements in discomfort (P=0.020), impact (P=0.0002), and total score (P=0.0005). The questionnaire score changes were also associated with a lower perceived risk of hypoglycemia and fewer daily-life associated issues with insulin glargine. Secondary: Not reported
Rosenstock et al. ⁸⁷ (2000) Insulin glargine HS	DB, MC, PG, RCT Patients with type 1 diabetes on basal-	N=256 4 weeks	Primary: FPG at study end point calculated as the mean of three	Primary: Adjusted mean FPG at end point was 9.2 mmol/L for the pooled insulin glargine groups and 11.3 mmol/L for the NPH group (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(containing 30 µg/mL zinc chloride)</p> <p>vs</p> <p>insulin glargine HS (containing 80 µg/mL zinc chloride)</p> <p>vs</p> <p>NPH insulin HS or BID</p>	<p>bolus multiple daily insulin regimen for at least 2 months, 18 to 70 years of age, had BMI 18 to 28 kg/m², HbA_{1c} <10.0%, postprandial serum C-peptide <0.2 pmol/mL</p>		<p>FPG values on days 27, 28 and 29</p> <p>Secondary: Change from baseline in overnight plasma glucose, mean FPG, blood glucose profile, nocturnal blood glucose, stability of FPG, HbA_{1c}, safety and adverse events</p>	<p>Secondary: The adjusted mean overnight plasma glucose levels after 5 AM were 7.8 mmol/L for insulin glargine 30, 7.3 mmol/L for insulin glargine 80, and 10.7 mmol/L for NPH (P values not reported).</p> <p>At the end of the study, the mean standard deviations for FPG were 7.6±2.3 and 7.5±1.9 mmol/L for the insulin glargine 30 and insulin glargine 80 groups, respectively, and 9.0±2.4 mmol/L for the NPH group (P<0.001).</p> <p>Blood glucose profile determined from seven self monitoring of blood glucose values during the day was not different among the treatment group (P value not reported).</p> <p>Nocturnal blood glucose measured by self monitoring of blood glucose at 3 AM was higher in the insulin glargine group than in the NPH group (P value not reported).</p> <p>Stability of FPG was significantly lower in patients receiving insulin glargine 30 compared to patients receiving NPH (P<0.05).</p> <p>The mean standard deviation for HbA_{1c} levels were -0.40±0.48 and -0.40±0.49 in the insulin glargine 30 and insulin glargine 80 groups, respectively, and -0.40±0.48 in the NPH group (P value not reported).</p> <p>Fewer patients receiving NPH (93.2%) reported a hypoglycemic episode than patients receiving insulin glargine (97.6 and 100% for insulin glargine 30 and insulin glargine 80, respectively; P=0.03). All events were considered mild and none resulted in discontinuation from study treatment.</p> <p>Insulin glargine was as safe as NPH with no differences between treatments with regard to the incidence of adverse effects, including the most frequent event, injection site reactions.</p>
<p>Rossetti et al.⁸⁸ (2003)</p> <p>Insulin glargine PM and insulin lispro</p>	<p>RCT</p> <p>Patients with type 1 diabetes and fasting plasma C-peptide</p>	<p>N=51</p> <p>12 weeks</p>	<p>Primary: HbA_{1c} level</p> <p>Secondary: Blood glucose</p>	<p>Primary: In patients taking NPH, HbA_{1c} increased slightly from baseline, but was not statistically significant. However, HbA_{1c} decreased both with the dinnertime as well as the bedtime dose of insulin glargine (P<0.04). There was no significant difference in the change of HbA_{1c} in both insulin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>before meals</p> <p>vs</p> <p>insulin glargine HS and insulin lispro before meals</p> <p>vs</p> <p>NPH insulin QD and insulin lispro before meals</p> <p>Glycemic targets were blood glucose 6.4 to 7.2 mmol/L in the fasting state, before meals, and at bedtime and blood glucose at 8.0 to 9.2 mmol/L 90 minutes after meals.</p>	<p>≤0.15 nmol/L on intensified treatment with multiple daily combinations of lispro and NPH at each meal and NPH at bedtime</p>		<p>profile from home blood glucose monitoring, hypoglycemia</p>	<p>glargine groups (P value NS).</p> <p>Secondary: Patients taking insulin glargine had lower blood glucose concentrations in the fasting state, after breakfast, before lunch, and after lunch (P<0.05). The before-dinner blood glucose with NPH and insulin glargine at dinnertime was similar (P value NS), but was lower with insulin glargine at bedtime (P<0.05). The after-dinner blood glucose was lower with insulin glargine at dinner-time and bedtime than with NPH (P<0.05). However, the bedtime blood glucose was not different with all three treatment groups (P value NS).</p> <p>The frequency of mild hypoglycemia was lower in patients taking insulin glargine than in patients taking NPH (P<0.005). There was no difference between the insulin glargine at dinnertime and insulin glargine at bedtime groups (P value NS). Patients taking insulin glargine had a lower frequency of nocturnal hypoglycemic episodes than patients taking NPH (P<0.05). There were no differences between both insulin glargine groups (P value NS).</p>
<p>Home et al.⁸⁹ (2015) EDITION 4</p> <p>Insulin glargine U-300 QAM</p> <p>vs</p> <p>Insulin glargine U-300 QPM</p> <p>vs</p>	<p>MC, PG, RCT</p> <p>Patients ≥18 years of age with a diagnosis of type 1 diabetes for at least one year, use of any mealtime insulin analog for ≥3 months</p>	<p>N=549</p> <p>6 months</p>	<p>Primary: HbA_{1c} change from baseline to month six</p> <p>Secondary: Percentage of participants attaining HbA_{1c} <7.0%, self-measured plasma glucose, hypoglycemia</p>	<p>Primary: The change in HbA_{1c} (primary end point; baseline 8.1%) was equivalent in the two treatment groups (difference, 0.04%; 95% CI, -0.10 to 0.19), and Gla-300 was thus noninferior. Similar results with wider 95% CIs were found for morning and evening injection times and for prebreakfast self-measured plasma glucose overall.</p> <p>Secondary: A similar percentage of participants in each overall group achieved HbA_{1c} <7.0% at month 6, 16.8% for Gla-300 and 15.0% for Gla-100. No relevant differences were observed in the change from baseline to month six in preinjection or within-participant variability of preinjection self-measured plasma glucose and the average of the 8-point self-measured plasma glucose estimations. Over six months, 255 people (93%) in the Gla-300</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>insulin glargine U-100 QAM</p> <p>vs</p> <p>insulin glargine U-100 QPM</p> <p>Mealttime insulin was continued and dose adjustments of basal insulin were made weekly.</p>				<p>group had one or more confirmed (≤ 70 mg/dL) or severe hypoglycemic events compared with 257 (94%) in the Gla-100 group. For nocturnal hypoglycemia, this was 188 (69%) and 193 (70%) of study participants.</p>
<p>Pesić et al.⁹⁰ (2007)</p> <p>Insulin glargine QD and insulin aspart before meals</p> <p>vs</p> <p>NPH insulin HS and insulin aspart before meals</p> <p>vs</p> <p>NPH insulin BID and insulin aspart before meals</p>	<p>RCT</p> <p>Patients with type 1 diabetes on long-term conventional insulin therapy</p>	<p>N=48</p> <p>12 weeks</p>	<p>Primary: Change in FPG, change in HbA_{1c}</p> <p>Secondary: Frequency of hypoglycemia</p>	<p>Primary: FPG was lower in the glargine group in comparison to the NPH BID group (7.30 vs 7.47 mmol/L, respectively), but this difference was not significant. FPG levels for the NPH-at-bedtime group were reported as significantly higher compared to either of the other two groups (8.44 mmol/L; P<0.05).</p> <p>At 12 weeks, HbA_{1c} decreased in both the NPH BID (from 7.80±0.83% to 7.01±0.63%) and insulin glargine groups (from 7.72±0.86% to 6.87±0.50%). However, there was no change in HbA_{1c} in the NPH-at-bedtime group.</p> <p>Secondary: A lower frequency of mild hypoglycemic episodes was observed in the insulin glargine group compared to both NPH groups (P<0.05).</p>
<p>Dundar et al.⁹¹ (2009)</p> <p>NPH QD</p>	<p>RETRO, XO</p> <p>Pediatric and adolescent patients with a mean age of</p>	<p>N=34</p> <p>12 months (6 months of NPH,</p>	<p>Primary: Mean total daily insulin dose, mean FPG, numbers of</p>	<p>Primary: Total daily insulin doses were similar among all three insulin groups (P>0.05 for all comparisons).</p> <p>No significant difference was seen in mean FPG between NPH and both</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>insulin detemir QD</p> <p>vs</p> <p>insulin glargine QD</p> <p>All patients received NPH insulin for ≥ 6 months before transitioning to either insulin detemir or insulin glargine at a dose that was 40 to 45% of total daily NPH insulin dose, in addition to insulin aspart TID at the same doses.</p>	<p>12.7\pm3.4 years, with type 1 diabetes for 5.4\pm3.0 years who were receiving NPH insulin daily and insulin aspart three times daily for ≥ 6 months</p>	<p>followed by 6 months of insulin detemir or insulin glargine)</p>	<p>severe and nocturnal hypoglycemia, mean HbA_{1c}, BMI SDS and safety</p> <p>Secondary: Not reported</p>	<p>long-acting insulins combined (P>0.05).</p> <p>Incidence of severe hypoglycemia with NPH was similar compared to insulin detemir and insulin glargine (P>0.05).</p> <p>Eight episodes of nocturnal hypoglycemia was reported in four patients during NPH treatment compared to three episodes reported in three patients in both long-acting insulin groups combined (P>0.05).</p> <p>Mean HbA_{1c} was significantly lower with insulin glargine and insulin detemir compared to NPH (P<0.05 for both). No significant difference was seen between insulin glargine and insulin detemir.</p> <p>The increase in BMI SDS was significantly lower with insulin detemir compared to the increase seen with NPH and insulin glargine (P<0.05 for both). No difference was noted between NPH and insulin glargine.</p> <p>No adverse events were reported during treatment with insulin glargine and insulin detemir.</p> <p>Secondary: Not reported</p>
<p>Chase et al.⁹² (2008)</p> <p>Insulin glargine AM and insulin lispro before meals</p> <p>vs</p> <p>NPH or Lente insulin BID (AM and PM) and insulin</p>	<p>AC, OL, PG, RCT</p> <p>Patients 9 to 17 years of age with type 1 diabetes with HbA_{1c} ≥ 7.0 to $\leq 9.5\%$, and receiving any daily insulin regimen consisting of ≥ 2 injections or a continuous infusion</p>	<p>N=175</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Incidence of hypoglycemia, safety</p>	<p>Primary: There was no difference in the decrease in HbA_{1c} with insulin glargine (-0.25%) and NPH (0.05%; P=0.1725). However, it was reported that the decrease in HbA_{1c} was significantly greater with insulin glargine in patients with higher baseline HbA_{1c}.</p> <p>Secondary: The incidence of hypoglycemia was significantly higher with insulin glargine (P=0.0298). There was no difference in the incidence of severe hypoglycemia between the two treatments.</p> <p>Both treatments were well tolerated and there was no difference in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>lispro before meals</p> <p>Basal insulin doses were titrated to achieve FPG 70 to 100 mg/dL.</p>				<p>rate of overall adverse events between them (P=0.1944). Metabolism and nutrition disorders (e.g., hypoglycemia, hyperglycemia, etc) were the most commonly reported treatment-emergent adverse events, and these occurred with comparable frequency between the two treatments (11.8 vs 5.6%; P=0.1803). Significantly more serious adverse events were reported with insulin glargine (P=0.0164).</p>
<p>Ahern et al.⁹³ (2002)</p> <p>Insulin pump therapy containing basal insulin</p> <p>The total patient population was stratified based on age: 1 to 6 years, 7 to 11 years, and 12 to 18 years.</p> <p>Patients were started on daily dose of insulin therapy prior to study start.</p> <p>The total daily dose was divided as 50% premeal bolus doses and 50% as basal replacement, given as a single hourly rate over the first 24 hours.</p>	<p>PRO</p> <p>Patients ≤18 years of age with type 1 diabetes, followed in children's diabetes clinic for at least 1 year prior to start of pump therapy, previously on a 2 to 3 injection/day regimen</p>	<p>N=161</p> <p>Average of 32±9 months</p>	<p>Primary: HbA_{1c}, diabetes-related adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: Patients in all three groups had good diabetes control prior to study start. However, HbA_{1c} levels fell by 0.6 to 0.7% in all three groups by 12 months. These levels were significantly lower than prepump levels (P≤0.02).</p> <p>Within each age group, the incidence of severe hypoglycemic events during pump therapy was lower than during prior injection therapy. The differences did not achieve statistical significance.</p> <p>When all three groups were combined, there was a significantly lower incidence of severe hypoglycemic events during the first 12 months of pump therapy than during the 12 months prior to pump therapy (P<0.05).</p> <p>Secondary: Not reported</p>
Intermediate-Acting and Long-Acting Insulins: Type 2 Diabetes Mellitus				
Zinman et al. ⁹⁴	MC, NI, OL, PG,	N=990	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2012) BEGIN: Once Long study</p> <p>Insulin degludec (FlexPen®) QD</p> <p>vs</p> <p>insulin glargine (SoloSTAR®) QD</p> <p>Patients in both treatment arms were also treated with metformin. Patients could also continue treatment with a DDP-4 inhibitor, but only 2% of evaluated patients utilized a DDP-4 inhibitor.</p>	<p>RCT</p> <p>Patients ≥18 years of age with a diagnosis of type 2 diabetes for ≥6 months, HbA_{1c} of 7% to 10%, BMI≤40 kg/m², treated with oral antidiabetic agents for at least three months prior to screening, and insulin treatment-naïve</p>	<p>52 weeks</p>	<p>Change in HbA_{1c} from baseline to week 52</p> <p>Secondary: Change from baseline in FPG and SMBG, patients with A_{1c} <7%, function health status, and safety</p>	<p>Mean HbA_{1c} decreased by 1.06% in the insulin degludec group and 1.19% in the insulin glargine group with an ETD of 0.09% (95% CI, -0.04 to 0.22; no P value reported).</p> <p>Secondary: FPG decreased from baseline to the end of the trial in both groups, with the most pronounced decline occurring during the first 12 weeks. Mean FPG levels decreased by 3.8 to 5.9 mmol/L in the degludec group and 3.3 to 6.4 mmol/L in the glargine group. There was a significant reduction in FPG in favor of the degludec group (ETD of -0.43 mmol/L [95% CI, -0.74 to -0.13; P=0.05]).</p> <p>The 9-point SMBG profiles appeared similar at baseline and decreased in both groups at the end of the trial</p> <p>Patients that achieved HbA_{1c} levels of <7% at the end of the trial were similar between groups, with 52% of patients in the degludec group and 54% of patients in the glargine group (P=0.40). There was also a similar proportions of participants achieved HbA_{1c} levels of <7% without confirmed hypoglycemia (degludec 42%; glargine 46%; P=0.34) and without nocturnal confirmed hypoglycemia (degludec 53%; glargine 54%; P=0.68) in the last 12 weeks of treatment.</p> <p>Rates of overall confirmed hypoglycemic episodes were similar (P=0.106) between treatment groups. The rate of nocturnal confirmed hypoglycemic episodes was significantly lower with degludec compared to glargine with an ERR of 0.64 (95% CI, 0.42 to 0.98; P=0.038). In specific analyses of the maintenance period (weeks 16 to 52), overall confirmed hypoglycemia rates were similar between treatments (P=0.067), and as with the overall rate, the rate of nocturnal confirmed hypoglycemia was significantly lower with degludec (P=0.004).</p>
<p>Rodbard et al.⁹⁵ (2013) BEGIN Once Long Study</p> <p>Insulin degludec</p>	<p>ES of a MC, NI, OL, PG, RCT (Zinman et al⁷⁵)</p> <p>Patients ≥18 years of age with a diagnosis</p>	<p>N=808</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 104</p> <p>Secondary:</p>	<p>Primary: In the extension trial set, after 104 weeks of treatment, the observed mean (SD) HbA_{1c} decreased from 65 ± 9 mmol/mol (8.1 ± 0.8%) at baseline to 53 ± 10 mmol/mol (7.0 ± 0.9%) with degludec and from 66 ± 9 mmol/mol (8.2 ± 0.8%) at baseline to 52 ± 9 mmol/mol (6.9 ± 0.8%) with glargine. There was no statistical difference between treatments with an</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(FlexPen[®]) QD vs insulin glargine (SoloSTAR[®]) QD</p> <p>Patients in both treatment arms were also treated with metformin. Patients could also continue treatment with a DDP-4 inhibitor, but only 2% of evaluated patients utilized a DDP-4 inhibitor.</p>	<p>of type 2 diabetes for ≥6 months, HbA_{1c} of 7% to 10%, BMI≤40 kg/m², treated with oral antidiabetic agents for at least three months prior to screening, and insulin treatment-naïve</p>		<p>Change from baseline in FPG and SMBG, patients with A_{1c} <7%, and safety</p>	<p>ETD of 0.07% (95% CI, -0.07 to 0.22; P=0.339).</p> <p>Secondary: Overall confirmed hypoglycemia rates were similar between degludec and glargine when considering the entire trial period (1.72 and 2.05 episodes/patient-year; estimated rate ratio of 0.84; 95% CI, 0.68 to 1.04; P=0.115) and maintenance period (1.80 and 2.21 episodes/patient-year; estimated rate ratio of 0.80; 95% CI, 0.63 to 1.01; P=0.063)</p> <p>Nocturnal confirmed hypoglycemia was significantly lower with degludec at end of trial compared with glargine (0.27 vs 0.46 episodes/patient-year; estimated rate ratio of 0.57 [95% CI, 0.40 to 0.81; P=0.002]) and significantly lower in the maintenance period (0.28 vs 0.53 episodes/patient-year; estimated rate ratio of 0.47 [95% CI, 0.32 to 0.69; P<0.001]).</p> <p>The rate of severe hypoglycemia was significantly lower with degludec than glargine when considering the entire trial period for the safety analysis set (0.006 vs 0.021 episodes/patient-year; estimated rate ratio of 0.31 [95% CI, 0.11 to 0.85; P=0.023]).</p> <p>The observed mean reduction in laboratory-measured fasting plasma glucose was significantly greater with degludec (4.17 mmol/L) than with glargine (3.56 mmol/L) with an ETD of -0.36 mmol/L (95% CI, -0.67 to -0.05; P=0.021). Similar results were seen in the extension trial set.</p> <p>The 9-point self-monitored blood glucose profiles were similar at baseline and at end of treatment for both treatments in both the full and extension trial sets. There were no significant differences in prandial increments.</p>
<p>Philis-Tsimikas et al.⁹⁶ (2013)</p> <p>Insulin degludec (FlexPen[®]) QD vs</p>	<p>AC, MC, PG, OL, RCT</p> <p>Patients ≥18 years of age with a diagnosis of type 2 diabetes for ≥6 months, insulin-naïve, HbA_{1c}</p>	<p>N=458 26 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 26</p> <p>Secondary: Change from baseline to week</p>	<p>Primary: Insulin degludec provided a statistically significant reduction in HbA_{1c} when compared to sitagliptin. After 26 weeks of treatment, mean HbA_{1c} was 7.2% in the insulin degludec group and 7.7% in the sitagliptin group. The ETD was -0.43% (95% CI, -0.61 to -0.24; no P value reported).</p> <p>Secondary: After 26 weeks, the observed mean FPG was 6.2 mmol/L (111.7 mg/dL)</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>sitagliptin 100 mg QD</p> <p>All patients received the active treatment in addition with one or two other oral antidiabetic agents in any combination (metformin, sulphonylureas, glinides, or pioglitazone)</p>	<p>7.5 to 11%, BMI ≤ 40 kg/m², treated with one or two oral antidiabetic agents (metformin, sulphonylureas or glinides or pioglitazone) with an unchanged dose for at least three months</p>		<p>26 in FPG, patients with HgA_{1c} <7%, patients with HgA_{1c} <7% and no hypoglycemic episodes, mean SMPG, prandial glucose, responders with HgA_{1c} <6.5%, HRQoL score</p>	<p>with insulin degludec and 8.5 mmol/L (153.2 mg/dL) with sitagliptin. The estimated mean change from baseline was -3.41 mmol/L (-61.4 mg/dL) with insulin degludec and -1.24 mmol/L (-22.3 mg/dL) with sitagliptin (ETD, -2.17 mmol/L; 95% CI, -2.59 to -1.74; no P value reported).</p> <p>Treatment with in insulin degludec showed a higher proportion of subjects achieving HbA_{1c} <7.0% at end of trial with 41% in the insulin degludec group and 28% in the sitagliptin group (OR, 1.60; 95% CI, 1.04 to 2.47; no P value reported).</p> <p>The proportion of subjects achieving HbA_{1c} <7.0% without hypoglycemia at end of trial was 25% in the insulin degludec group an 23% in the sitagliptin (OR, 0.92; 95% CI, 0.55 to 1.53; no P value reported).</p> <p>The observed proportion of subjects achieving HbA_{1c} $\leq 6.5\%$ at end of trial was 28.0% with insulin degludec and 14.9% with sitagliptin (OR, 1.98; 95% CI, 1.17 to 3.33; no P value reported).</p> <p>At all time-points in the 9-point profile, the estimated mean SMPG value was lower for insulin degludec compared to sitagliptin after 26 weeks of treatment. The estimated mean of the overall 9-point profile was lower with insulin degludec than with sitagliptin (ETD -1.31 mmol/l; 95% CI, -1.69 to -0.94; No P value reported).</p> <p>The prandial glucose increment, defined as the difference in SMPG values 90 min before and after a meal, was seen to be higher with insulin degludec compared to sitagliptin across 'all meals' and at breakfast after 26 weeks; the ETD was 0.35 mmol/L (95% CI, 0.05 to 0.65; no P value reported) for 'all meals' and 0.54 mmol/L (95% CI, 0.07 to 1.02; no P value reported) for breakfast.</p> <p>The change in nocturnal prandial glucose was greater with insulin degludec than with sitagliptin from bedtime to breakfast; with an ETD of -0.94 mmol/L (95% CI, -1.43 to -0.46; no P value reported).</p> <p>The patient-reported outcome results appeared to be similar between the two treatment groups for the DPM, SF-36 v2 and Hypoglycemic</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Episode—Interview Questionnaire, with only marginal changes over time.</p> <p>The rate of confirmed hypoglycemic episodes was higher with insulin degludec compared with sitagliptin (3.07 vs 1.26 episodes per patient-year; no P value reported). There was no difference between treatment groups in the rate of nocturnal confirmed hypoglycemic episodes with 0.52 and 0.30 episodes per patient-year for insulin degludec and sitagliptin groups, respectively. Only one episode of severe hypoglycemia occurred during the study (insulin degludec group) with a rate of 0.01 episodes per patient-year.</p> <p>Patients treated with a sulphonylurea or pioglitazone had an increased rate of hypoglycemic episodes than those that did not for both groups. Patients in the insulin degludec arm who received a sulphonylurea or pioglitazone had a hypoglycemic episode rate of 3.43 compared with a rate of 1.71 in patients who did not. In the sitagliptin group, patients who were also treated with a sulphonylurea or pioglitazone had a rate of 1.92 whereas patients treated without had a rate of 0.00.</p>
<p>Meneghini et al.⁹⁷ (2013)</p> <p>Insulin degludec (FlexPen®) QD (forced-flex dosing)</p> <p>vs</p> <p>Insulin degludec (FlexPen®) QD (same-time dosing)</p> <p>vs</p> <p>insulin glargine</p>	<p>MC, NI, OL, PG, RCT</p> <p>Patients ≥18 years of age with a diagnosis of type 2 diabetes for ≥6 months, BMI of ≤40 kg/m², and previously treated with either oral antidiabetic drugs (baseline HbA_{1c} = 7.0 to 11.0%) or, any basal insulin ± oral antidiabetic agents (baseline HbA_{1c} = 7.0 to 10.0%)</p>	<p>N=687</p> <p>26 weeks</p>	<p>Primary: Change in HgA_{1c} from baseline to week 26</p> <p>Secondary: Patients with HgA_{1c} <7%, change from baseline in FPG and SMPG, safety</p>	<p>Primary: Mean HbA_{1c} changes from baseline to week 26 were similar between treatment groups. Observed mean decreases were -1.28% (degludec forced-flex), -1.07% (degludec same-time), and -1.26% (glargine same-time). ETD between degludec (forced-flex) and glargine groups was 0.04% (95% CI, -0.12 to 0.20). ETD between degludec (forced-flex) and degludec (same-time) groups not significant (-0.13%; 95% CI, -0.29 to 0.03).</p> <p>Secondary: After 26 weeks of treatment, similar proportions of participants had achieved an HbA_{1c} of <7.0% with degludec (forced-flex) and glargine (same-time) groups (38.9% vs 43.9%, P=0.34); likewise, no statistically significant difference in HbA_{1c} was found between the degludec (forced-flex) and degludec (same-time) groups (38.9% vs 40.8%, P=0.99).</p> <p>Mean laboratory-measured FPG values decreased in all treatment groups. At the end of the trial, the observed mean FPG concentration was 5.8</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(SoloSTAR[®]) QD (same-time dosing)</p> <p>Patients continued oral antidiabetic agents currently prescribed</p>				<p>mmol/L for both degludec groups and 6.2 mmol/L for the glargine group. Insulin degludec (forced-flex) was associated with a significantly greater reduction in FPG than glargine (same-time) after 26 weeks of treatment (ETD, -0.42 mmol/L; 95% CI, -0.82 to -0.02; P=0.04). There was no significant difference between the degludec groups (ETD, -0.05 mmol/L; 95% CI, -0.45 to 0.35; P value not reported).</p> <p>After 26 weeks, mean 9-point SMPG profiles were similar for the three treatment groups and decreased compared with corresponding mean profiles at baseline.</p> <p>A similar proportion of participants (44 to 51%) reported confirmed hypoglycemia in the three treatment groups. There was no significant differences found between the insulin degludec (forced-flex) and insulin glargine (same-time) groups with respect to the rates of overall confirmed hypoglycemia and nocturnal confirmed hypoglycemia. There was no significant difference in hypoglycemia rates when both degludec groups were compared.</p>
<p>Garber et al.⁹⁸ (2012) BEGIN Basal-Bolus Type 2 study</p> <p>Insulin degludec (FlexPen[®]) QD + insulin aspart at meal time</p> <p>vs</p> <p>insulin glargine (SoloSTAR[®]) QD + insulin aspart at meal time</p> <p>Patients may also</p>	<p>MC, NI, OL, PG, RCT</p> <p>Patients ≥18 years of age with a diagnosis of diabetes type 2 for ≥6 months, HbA_{1c} of 7 to 10%, BMI ≤40 mg/m², treated with any insulin-containing regimen for at least three months (with or without oral agents)</p>	<p>N=1,006</p> <p>52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to 52 weeks</p> <p>Secondary: FPG, SMPG, prandial plasma glucose increment, HRQoL, safety</p>	<p>Primary: The estimated mean change from baseline in HbA_{1c} was -1.10% with insulin degludec and -1.18% with insulin glargine with an ETD of 0.08% (95% CI, -0.05 to 0.21).</p> <p>Secondary: Concentrations of FPG decreased by 2.3 mmol/L with insulin degludec and 2.0 mmol/L with insulin glargine (ETD -0.29 mmol/L; 95% CI, -0.65 to 0.06; P=0.1075).</p> <p>The 9-point SMPG profiles seemed similar for the two treatment groups at baseline and decreased in both groups by week 52 (no P values reported). After 52 weeks, mean prandial increments were similar between treatment groups for all meals (no P values reported).</p> <p>The HRQoL questionnaire showed a significant difference between treatment groups in favor of insulin degludec compared with insulin glargine for the SF-36 domain of bodily pain (P=0.0320). No other results for HRQoL SF-36 domains provided in the primary publication.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>be treated with metformin, pioglitazone or both</p>				<p>Rates of overall, nocturnal, and diurnal confirmed hypoglycemia were significantly lower in patients treated with insulin degludec than with insulin glargine. Rates of overall confirmed hypoglycemia were 11.09 episodes per patient-year exposure with insulin degludec and 13.63 with insulin glargine; the estimated rate ratio was 0.82 (95% CI, 0.69 to 0.99; P=0.0359) in favor of insulin degludec. Too few severe hypoglycemic events occurred for differences between groups to be assessed. The proportions of participants with confirmed hypoglycemic events were similar with insulin degludec (609 [81%] of 753 participants) and insulin glargine (206 [82%] of 251 participants). The rate of nocturnal confirmed hypoglycemia was 1.39 episodes per patient-year exposure for insulin degludec and 1.84 for insulin glargine. The rate ratio for nocturnal confirmed hypoglycemic episodes was 0.75 (95% CI, 0.58 to 0.99; P=0.0399) in favor of insulin degludec.</p>
<p>Hollander et al.⁹⁹ (2015) BEGIN Basal-Bolus Type 2 study Insulin degludec (FlexPen[®]) QD + insulin aspart at meal time vs insulin glargine (SoloSTAR[®]) QD + insulin aspart at meal time Patients may also be treated with metformin, pioglitazone or both</p>	<p>ES of a MC, NI, OL, PG, RCT (Garber et al) Patients ≥18 years of age with a diagnosis of diabetes type 2 for ≥6 months, HbA_{1c} of 7 to 10%, BMI ≤40 mg/m², treated with any insulin-containing regimen for at least three months (with or without oral agents)</p>	<p>N=1,006 78 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to 52 weeks Secondary: FPG, SMPG, prandial plasma glucose increment, HRQoL, safety</p>	<p>Primary: In the extension trial population, the mean HbA_{1c} value decreased from 8.2% at baseline to 7.2% after 78 weeks of treatment with insulin degludec and from 8.3% to 7.1% with insulin glargine (ETD of 0.14%; 95% CI, -0.01 to 0.30; P value not reported). In the full analysis set population, the mean HbA_{1c} value decreased from 8.3% at baseline to 7.3% with insulin degludec and from 8.4% to 7.2% with insulin glargine (ETD 0.16%; 95% CI, 0.02 to 0.30; P=0.022). The FPG level decreased by 2.4 mmol/L (43 mg/dL) after 78 weeks of treatment with insulin degludec and by 2.2 mmol/L (40 mg/dL) after treatment with insulin glargine in the extension trial set population (ETD was -0.19 mmol/L; 95% CI, -0.59 to 0.21; P value not reported). Similar results were obtained in the full analysis set population. The ERR of overall confirmed hypoglycemia in the extension trial set for comparing the insulin degludec groups compared to the insulin glargine group was 0.76 (95% CI, 0.62 to 0.94; P=0.011). In the full analysis set population, the rates of overall confirmed hypoglycemia were not significantly different between the insulin degludec and insulin glargine groups (ERR, 0.85; 95% CI, 0.70 to 1.02; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>The ERR of nocturnal confirmed hypoglycemia in the extension trial set for comparing the insulin degludec groups compared to the insulin glargine group was 0.69 (95% CI, 0.51 to 0.93; P=0.016). Lower rates of nocturnal hypoglycemia were also observed with insulin degludec in the full analysis set (ERR, 0.76; 95% CI, 0.58 to 1.00; P=0.047).</p> <p>The estimated rates of severe hypoglycemia were low and not significantly different between insulin degludec and insulin glargine in both the extension trial set (ERR, 0.66; 95% CI 0.31 to 1.37; P value not reported) and the full analysis set populations (ERR, 0.83; 95% CI 0.43 to 1.61; P value not reported).</p>
<p>Gough et al.¹⁰⁰ (2013)</p> <p>Insulin degludec 200 units/mL (FlexTouch®) QD</p> <p>vs</p> <p>insulin glargine (SoloSTAR®) QD</p> <p>Patients were continued on metformin. If DPP-4 inhibitors were labeled for use in combination with insulin, patients continued their DPP-4 inhibitor, otherwise it was also discontinued</p>	<p>MC, NI, OL, PG, RCT</p> <p>Patients ≥18 years of age, diagnosis of type 2 diabetes for ≥6 months, HbA_{1c} 7 to 10%, BMI ≤45 kg/m², previous treatment with metformin with or without additional oral antidiabetic drugs for ≥3 months</p>	<p>N=457</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to 26 weeks</p> <p>Secondary: Number of treatment-emergent confirmed hypoglycemic episodes, change from baseline in FPG, SMBG frequency of patients reaching A_{1c} <7%</p>	<p>Primary: Change in HbA_{1c} from baseline, improved with both insulin degludec 200 units/mL and insulin glargine after 26 weeks of treatment. Mean HbA_{1c} decreased by 1.3 ± 1.01% (14.3 ± 11.0 mmol/mol, mean ± SD) for both treatment groups, with an ETD of 0.04 (95% CI, -0.11 to 0.19).</p> <p>Secondary: There was no significant difference in the proportion of participants that achieved the HbA_{1c} target of <7% between insulin degludec 200 units/mL with 52% and insulin glargine with 56% (OR, 0.85; 95% CI, 0.56 to 1.30).</p> <p>Insulin degludec 200 units/mL resulted in a statistically significantly greater FPG reduction than insulin glargine after 26 weeks of treatment. The ETD between groups was -0.42 (95% CI, -0.78 to -0.06; no P value reported). Overall, the 9-point SMBG profiles decreased in both treatment groups and were similar after 26 weeks.</p> <p>No subjects in either of the treatment groups reported episodes of severe hypoglycemia. The proportion of patients that experienced a confirmed episode of hypoglycemia was 28.5% for insulin degludec and 30.7% for insulin glargine. Event rates were 1.22 and 1.42 episodes/patient-year, respectively (ERR, 0.86; 95% CI, 0.58 to 1.28; P=0.46). A total of 6.1% and 8.8% of participants in the insulin degludec 200 units/mL and insulin glargine experienced nocturnal confirmed hypoglycemic episodes with rates of 0.18 and 0.28 episodes/patient-year, respectively (ERR, 0.64, 95%</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Meneghini et al.¹⁰¹ (2007)</p> <p>Insulin detemir±oral antidiabetic drug transferred from 3 groups of patients: oral antidiabetic drug only, NPH±oral antidiabetic drug, insulin glargine±oral antidiabetic drug</p>	<p>OL, OS</p> <p>Subgroup of patients with type 2 diabetes from the German cohort of PREDICTIVE study</p>	<p>N=1,832</p> <p>12 weeks</p>	<p>Primary: Incidence of severe adverse drug reactions (severe adverse drug reactions) (major hypoglycemic events)</p> <p>Secondary: Hypoglycemic events, weight changes, HbA_{1c}, FPG</p>	<p>CI, 0.30 to 1.37, P=0.25).</p> <p>Primary: No severe adverse drug reactions were reported during the 12 week follow-up. Reports of adverse drug reactions occurred in 0.3% of patients, including one report of drug intolerance, two diabetes-related reports, one report of headache, and one report of skin allergy (P values were not reported).</p> <p>Secondary: The percentage of patients experiencing hypoglycemia and the frequency of hypoglycemic episodes were lower in the insulin detemir group during the four weeks preceding the follow-up visit compared to baseline. The total, daytime, and nocturnal hypoglycemic events at baseline decreased from 3.3, 2.0, and 1.3 events/patient-year, respectively, to -2.7, -1.6, and -1.2, respectively (P<0.0001). The percentage of patients experiencing these events decreased from 7.2, 5.5, and 3.7%, respectively, to 2.0, 1.6, and 0.5% at follow-up (P values not reported).</p> <p>There were overall reductions in body weight following the transition to insulin detemir (P<0.0001). All three groups of patients had weight reduction after initiating insulin detemir (P<0.0001 in the oral antidiabetic drug only group, P<0.0099 in the NPH±oral antidiabetic drug group, and P<0.0001 in the insulin glargine±oral antidiabetic drug group).</p> <p>A reduction of -1.1±0.03% in mean HbA_{1c} was observed at study endpoint (P<0.0001). Patients that were in the oral antidiabetic drug only group had a reduction of -1.29±0.03% (P<0.0001) from baseline, which was a slightly greater reduction than in the NPH±oral antidiabetic drug and insulin glargine±oral antidiabetic drug groups (-0.60±0.09% and -0.59±0.06%, respectively; P<0.0001 for both).</p> <p>There was a significant reduction in mean FPG overall (P<0.0001). However, patients transitioning from the oral antidiabetic drug only group tended to have a greater reduction in FPG from baseline than those transitioning from the other two treatment regimens (P<0.0001).</p>
<p>Hollander et al.¹⁰² (2008)</p>	<p>MC, NI, OL, PG, RCT</p>	<p>N=319</p>	<p>Primary: HbA_{1c} at 52</p>	<p>Primary: Mean HbA_{1c} at 52 weeks was 7.19% with insulin detemir and 7.03% with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin detemir PM or BID (AM and PM) and insulin aspart before meals</p> <p>vs</p> <p>insulin glargine PM and insulin aspart before meals</p> <p>Basal insulin doses were titrated to achieve pre-breakfast and pre-dinner PG ≤ 108 mg/dL.</p> <p>Prandial insulin doses were titrated to achieve PPG ≤ 162 mg/dL.</p> <p>Insulin secretagogues and α-glucosidase inhibitors were discontinued.</p> <p>United States patients on TZDs were allowed to continue treatment.</p>	<p>Patients ≥ 18 years of age with type 2 diabetes for ≥ 1 year who were receiving oral diabetic medications or insulin with or without oral diabetes medications for >4 months with HbA_{1c} 7.0 to 11.0% and BMI ≤ 40 kg/m²</p>	<p>52 weeks</p>	<p>weeks</p> <p>Secondary: Change in body weight, proportion of patients achieving HbA_{1c} $\leq 7.0\%$ with or without major hypoglycemia in the last three months of treatment, FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose, 10-point self-monitored plasma glucose profiles and safety</p>	<p>insulin glargine (mean difference, 0.17; 95% CI, -0.07 to 0.40), meeting the prespecified non-inferiority margin.</p> <p>Secondary: Patients receiving insulin detemir experienced significantly less weight gain compared to those receiving insulin glargine (2.8 vs 3.8 kg; P<0.05).</p> <p>Similar percentage of patients achieved HbA_{1c} $\leq 7.0\%$ with insulin detemir compared to insulin glargine (36.2 vs 36.7%; P value NS). The HbA_{1c} goal was achieved without symptomatic hypoglycemia in 17.1 and 21.4% of patients in the insulin detemir and insulin glargine groups, respectively (P value NS).</p> <p>No significant differences were observed between the two groups with regard to FPG at the end of study, changes in FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose and 10-point self-monitored plasma glucose profiles.</p> <p>Episodes of major hypoglycemia were reported in 4.7 and 5.7% of patients in the insulin detemir and insulin glargine groups, respectively (P=0.588). Incidence of nocturnal and symptomatic hypoglycemia was also comparable between the two groups (P>0.05 for both).</p> <p>Severe treatment-emergent adverse events were reported in 13.6 and 19.0% of patients in the insulin detemir and insulin glargine groups.</p>
<p>Raskin et al.¹⁰³ (2009)</p>	<p>MC, NI, OL, PG, RCT</p>	<p>N=385</p> <p>26 weeks</p>	<p>Primary: HbA_{1c} at 26 weeks</p>	<p>Primary: The least squared mean change in HbA_{1c} from baseline at 26 weeks was -1.08% with insulin detemir and -1.28% with insulin glargine (difference,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin detemir PM or BID (AM and PM) and insulin aspart before meals (IDet)</p> <p>vs</p> <p>insulin glargine PM and insulin aspart before meals (IGla)</p> <p>Basal insulin doses were titrated to achieve pre-breakfast PG \leq108 mg/dL.</p> <p>Treatment with insulin secretagogues and α-glucosidase inhibitors were discontinued.</p> <p>Treatment with TZDs and metformin was continued.</p>	<p>Patients \geq18 years of age with type 2 diabetes who previously received any oral diabetes medication or insulin with or without oral diabetes medications with HbA_{1c} 7.0 to 11.0% and BMI \leq40 kg/m²</p>		<p>Secondary: FPG, body weight, safety</p>	<p>0.207; 95% CI, 0.0149 to 0.3995; P=0.035), showing non-inferiority.</p> <p>When last observation carried forward analysis was used, the least squared mean change in HbA_{1c} was -0.94 and -1.25% with insulin detemir and insulin glargine, respectively. The difference between the two groups (0.307; 95% CI, 0.1023 to 0.5109; P=0.004) was inconclusive regarding possible inferiority of insulin detemir since the 95% CI included 0.4, the prespecified inferiority margin.</p> <p>Secondary: No significant differences were seen in change in FPG from baseline at 26 weeks between the two treatment groups.</p> <p>Patients in the insulin detemir group experienced less weight gain compared to those in the insulin glargine group (1.20\pm3.96 vs 2.70\pm3.94 kg; P=0.001).</p> <p>Rates of overall, nocturnal and major hypoglycemic events were comparable between the two groups. Sixty-six percent of patients in the insulin detemir group and 71% in the insulin glargine group reported treatment-emergent adverse events.</p>
<p>Rosenstock et al.¹⁰⁴ (2008)</p> <p>Insulin detemir PM or BID (AM and HS)</p> <p>vs</p>	<p>MC, NI, OL, PG, RCT</p> <p>Insulin-naïve type 2 diabetics \geq18 years of age, receiving oral antidiabetic agents, with HbA_{1c}</p>	<p>N=582</p> <p>52 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline plasma glucose and body weight,</p>	<p>Primary: Decreases in HbA_{1c} were -1.5% with both treatments and were comparable after 52 weeks at 7.2 and 7.1% (difference, 0.05%; 95% CI, -0.11 to 0.21), thereby meeting the criteria for non-inferiority for insulin detemir vs insulin glargine.</p> <p>Secondary: Within-patient variation of self-monitored plasma glucose pre-breakfast</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>insulin glargine HS</p> <p>Basal insulin doses were titrated to achieve FPG \leq6 mmol/L.</p> <p>Existing oral antidiabetic drug therapy was continued.</p>	<p>7.5 to 10.0%, and BMI \leq40.0 kg/m²</p>		<p>proportion of patients achieving HbA_{1c} \leq7.0% without hypoglycemia, incidence of hypoglycemia, safety</p>	<p>and -dinner did not differ significantly between the two treatments. The overall shape of the 10-point self-monitored plasma glucose profile during the last week of treatment was similar between the two treatments (P value NS).</p> <p>Weight gain was significantly less with insulin detemir compared to insulin glargine (3.0 vs 3.9 kg; P=0.01).</p> <p>With both treatments, 52% of patients achieved HbA_{1c} \leq7.0%, with 33 and 35% of patients receiving insulin detemir and insulin glargine doing so without hypoglycemia (P value not reported).</p> <p>The risk of hypoglycemia of any type was comparable between the two treatments. The overall rate was low at 5.8 vs 6.2 episodes per patient-year with insulin detemir vs insulin glargine (RR, 0.94; 95% CI, 0.71 to 1.25), while the rate of nocturnal hypoglycemia was 1.3 episodes per patient-year with both treatments.</p> <p>Serious adverse events were less frequent with insulin detemir (42 patients with 47 events vs 53 patients with 73 events; P value not reported). One death was reported with insulin detemir (cause and/or reason unknown). Adverse events recorded as serious tended to be of a wide-ranging disparate nature, with no clear pattern of between-treatment differences. The only differences in adverse events were injection-site disorders (4.5 vs 1.4%), allergic reactions (3 vs 1 patients), and skin disorders including pruritus and rash (6 vs 1 patients).</p>
<p>King¹⁰⁵ (2009)</p> <p>Insulin detemir SC QD</p> <p>vs</p> <p>insulin glargine SC QD</p>	<p>DB, RCT, XO</p> <p>Type 2 diabetics receiving oral antidiabetic agents</p>	<p>N=36</p> <p>24 hours</p>	<p>Primary: 24-hour glycemic control, time to basal glycemic control, insulin dose</p> <p>Secondary: Not reported</p>	<p>Primary: Glucose profiles for each hour were similar between the two treatments. Glucose values for each five minute interval for insulin detemir during the basal period, the period 12 hours after injection, and overall 24-hour period were similar to insulin glargine.</p> <p>The AUC for the self-monitored glucose levels over 24 hours was 293.2 and 3,114.5 mg.h/dL (point ratio, 0.941; 90% CI, 0.885 to 1.001); therefore, the two treatments were considered bioequivalent for 24-hour glucose.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Once the patient achieved 2 consecutive days at goal, the insulin treatment was switched to the other agent.</p>				<p>Target basal glycemic control was achieved in all patients in 3.8 and 3.5 days with insulin detemir and insulin glargine ($P=0.360$).</p> <p>The dose of insulin detemir was similar to that of insulin glargine (26.3 and 22.6 units/day; $P=0.837$). Approximately one percent of all glucose values during the basal period were <70 mg/dL.</p> <p>Secondary: Not reported</p>
<p>Meneghini et al.¹⁰⁶ (2013)</p> <p>Insulin detemir vs insulin glargine</p> <p>Treat-to-target with weekly titrations</p>	<p>OL, RCT</p> <p>Insulin-naïve adults with type 2 diabetes on a stable dose of metformin ≥ 1500 mg with an HbA_{1c} of 7 to 9%</p>	<p>N=457</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Proportion of subjects achieving HbA_{1c} levels ≤ 7 or $\leq 6.5\%$ at 26 weeks, and the proportions achieving this without symptomatic hypoglycemia during the last month of treatment; safety</p>	<p>Primary: The observed mean HbA_{1c} reductions with detemir and glargine from baseline were 0.48% and 0.74% to end-of-study values of 7.48% and 7.13%, respectively. The estimated between-treatment difference (detemir–glargine) was 0.30% (95% CI, 0.14 to 0.46%) in the full analysis set and 0.35% (95% CI, 0.19 to 0.51%) in the per protocol analysis set. As the upper 95% CI values exceeded 0.4%, non-inferiority for detemir could not be confirmed.</p> <p>Secondary: The proportions of patients reaching HbA_{1c} $\leq 7\%$ at 26 weeks were 38% (80/209) and 53% (107/204) ($P=0.026$) in the detemir and glargine groups, respectively; whereas for patients reaching HbA_{1c} $\leq 7\%$ without hypoglycemia in the last four weeks, there was no significant difference between the treatments (32 and 38%, respectively; $P=0.438$). HbA_{1c} $\leq 6.5\%$ was attained by 11 and 21% in the detemir and glargine groups, respectively ($P=0.011$), 8.6% and 15.2% without hypoglycemia ($P=0.073$).</p> <p>The overall rate of hypoglycemia was low, with fewer than five episodes per subject-year in either treatment arm; the only two major events reported occurred with glargine. There was a significantly lower (27%) rate of all hypoglycemic episodes with detemir versus glargine, with no difference in the rate of nocturnal hypoglycemia</p> <p>Weight decreased slightly with detemir and increased slightly with glargine. Observed mean weight change was -0.49 kg with detemir and $+1.0$ kg with glargine, with a statistically significant estimated treatment difference of -1.5 kg (95% CI, -2.17 to -0.89 kg) in favor of detemir.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Liebl et al.¹⁰⁷ (2009)</p> <p>Insulin detemir PM and insulin aspart before meals</p> <p>vs</p> <p>biphasic insulin aspart 30 (consisting of 30% insulin aspart and 70% protamine-crystallized insulin aspart) BID</p> <p>Insulin detemir doses were titrated to achieve pre-breakfast PG 72 to 126 mg/dL and insulin aspart doses were titrated to achieve PPG \leq180 mg/dL.</p> <p>Biphasic insulin aspart doses were titrated to achieve pre-breakfast and pre-dinner plasma glucose 72 to 126 mg/dL.</p> <p>All oral antidiabetic drugs were</p>	<p>MC, RCT</p> <p>Adult type 2 diabetics \geq6 months, BMI \leq40 kg/m², currently receiving 1 or 2 oral antidiabetic agents, with or without concomitant QD intermediate- or long-acting insulin, and HbA_{1c} \geq7.0 to \leq12.0%</p>	<p>N=719</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving HbA_{1c} \leq7.0%; change in baseline FPG and body weight, self-monitored glucose prolife, incidence of hypoglycemia</p>	<p>Primary: Insulin detemir plus insulin aspart significantly decreased HbA_{1c} compared to biphasic aspart 30 (-1.56 vs -1.23%; treatment difference, 0.234%; 95% CI, 0.398 to -0.070; P=0.0052). Final HbA_{1c} values were 6.96 and 7.17%.</p> <p>Secondary: After 26 weeks, 60 and 50% of patients achieved HbA_{1c} \leq7.0% with insulin detemir plus insulin aspart and biphasic aspart 30 (P value not reported). Patients previously receiving basal insulin had significantly greater decrease with insulin detemir plus insulin aspart (-1.21 vs -0.75%; P=0.0129), whereas insulin-naïve patients had similar decreases (-1.69 vs -1.42%; P=0.106).</p> <p>There was no difference in the decrease of FPG between the two treatments (-52.3 vs -51.8 mg/dL; P=0.345).</p> <p>There was no difference in the amount of weight gain between the two treatments (4.1 vs 4.0 kg; P value not reported).</p> <p>Daily glucose profiles indicate that both treatments decrease glucose levels throughout the day. PPG was significantly lower with insulin detemir plus insulin aspart compared to biphasic aspart 30 (after breakfast; P=0.012, after lunch; P<0.001, and after dinner; P<0.001).</p> <p>A total of five and zero patients experienced major hypoglycemia with insulin detemir plus insulin aspart compared to biphasic aspart 30 (P value not reported). The rate of minor hypoglycemia was 31 vs 28%; P=0.837). The rate of nocturnal minor hypoglycemia was similar between the two treatments (7.4 vs 7.3%; P=0.666).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
discontinued to compare two insulin regimens.				
<p>Haak et al.¹⁰⁸ (2005)</p> <p>Insulin detemir HS and insulin aspart before meals</p> <p>vs</p> <p>NPH insulin HS and insulin aspart before meals</p> <p>Insulin doses were adjusted to achieve an FBG goal 4.0 to 7.0 mmol/L, PPG goal <10 mmol/L, and nocturnal goal of 4 to 7 mmol/L.</p>	<p>MC, OL, PG, RCT</p> <p>Patients aged ≥35 years of age with type 2 diabetes for ≥12 months, HbA_{1c} ≤12.0% and who had received insulin treatment for ≥2 months</p>	<p>N=505</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c} and FPG from baseline, nine-point self monitoring of blood glucose profile, hypoglycemia, weight gain</p> <p>Secondary: Not reported</p>	<p>Primary: At 26 weeks, significant HbA_{1c} reductions were observed with both the insulin detemir group (-0.2%; P=0.004) and the NPH group (-0.4%; P=0.0001). There was no significant difference in HbA_{1c} reduction between the two groups (P value not reported).</p> <p>At 26 weeks, both the insulin detemir group and NPH group had significant reductions in FPG from baseline (P=0.027 and P=0.026, respectively). However, differences between groups were NS (P=0.66).</p> <p>There were no significant differences in mean nine-point self monitoring of blood glucose profiles between the two groups (P=0.58).</p> <p>There was no significant difference in both nocturnal and total hypoglycemia between insulin detemir and NPH (P=0.95 and P=0.48, respectively).</p> <p>At 26 weeks, body weight changes from baseline were significantly lower with insulin detemir compared to NPH (1.0 vs 1.8 kg, respectively; P=0.017).</p> <p>Secondary: Not reported</p>
<p>Fajardo Montañana et al.¹⁰⁹ (2008)</p> <p>Insulin detemir HS and insulin aspart before meals</p> <p>vs</p> <p>NPH insulin HS</p>	<p>RCT, OL, PG, MC</p> <p>Patients ≥18 years of age with type 2 diabetes, HbA_{1c} 7.5 to 11.0%, BMI 25 to 40 kg/m², who were receiving two daily doses of insulin (at least one of them a premix) for ≥3</p>	<p>N=277</p> <p>26 weeks</p>	<p>Primary: Weight changes after 26 weeks</p> <p>Secondary: HbA_{1c} and FPG, proportion of patients achieving HbA_{1c} ≤7.0% without hypoglycemia</p>	<p>Primary: Mean weight gain at week 26 in the ITT population was significantly lower with insulin detemir (0.4 kg) than with NPH insulin (1.9 kg; P≤0.0001). In the PP analysis, there were similar changes in weight (0.4 kg with insulin detemir and 2.0 kg with NPH insulin; P≤0.0001).</p> <p>BMI increased less with insulin detemir (0.2 kg/m²) than with NPH insulin (0.8 kg/m²; P≤0.0001).</p> <p>Overall, 46.4% of insulin detemir patients showed no change or weight loss compared with 22.6% of NPH insulin patients.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>and insulin aspart before meals</p> <p>Basal insulin doses were titrated to achieve pre-breakfast PG ≤ 6.1 mmol/L.</p> <p>Insulin aspart doses were titrated to achieve PPG ≤ 10.0 mmol/L.</p> <p>Metformin therapy could be continued.</p>	<p>months; patients could also be receiving treatment with metformin; patients on other oral antidiabetic drugs were excluded</p>		<p>during the last four weeks of treatment, intra-subject variability in FPG, hypoglycemia</p>	<p>Secondary:</p> <p>At week 26, HbA_{1c} decreased from 8.9 to 7.8% in the insulin detemir group and from 8.8 to 7.8% in the NPH group (P=NS).</p> <p>FPG decreased from 10.8 to 8.8 mmol/L in the insulin detemir group and from 10.1 to 8.9 mmol/L in the NPH insulin group (P=NS).</p> <p>The proportion of patients achieving an HbA_{1c} $\leq 7.0\%$ without hypoglycemia during the last four weeks of treatment was 27% in both treatment groups (P=NS).</p> <p>Intra-subject variability of self-measured FPG at 26 weeks was lower with insulin detemir than with NPH insulin (P<0.0001).</p> <p>Patients in the insulin detemir group experienced significantly less hypoglycemia than patients in the NPH insulin group. Hypoglycemia was reported by 34.7% of patients treated with insulin detemir and by 65.3% of patients receiving NPH insulin. Nocturnal hypoglycemia was reported in 30.1% of insulin detemir patients and 69.9% of NPH insulin patients (RR 0.62 for all hypoglycemic events and 0.43 for nocturnal events; P<0.0001 for both).</p>
<p>Philis-Tsimikas et al.¹¹⁰ (2006)</p> <p>Insulin detemir PM</p> <p>vs</p> <p>insulin detemir AM</p> <p>vs</p> <p>NPH insulin PM</p>	<p>MC, OL, PG, RCT</p> <p>Men and women ≥ 18 years of age, had a BMI ≤ 40 kg/m², type 2 diabetes for ≥ 12 months, insulin naïve, HbA_{1c} 7.5 to 11.0% following at least 3 months of treatment with ≥ 1 oral antidiabetic drug</p>	<p>N=498</p> <p>20 weeks</p>	<p>Primary:</p> <p>Change in HbA_{1c} from baseline</p> <p>Secondary:</p> <p>Change in FPG, nine-point self monitoring of blood glucose profile, hypoglycemia</p>	<p>Primary:</p> <p>Both insulin detemir groups had similar reductions in HbA_{1c} compared to that of the NPH group. At 20 weeks, both evening and morning insulin detemir was found to be as effective as evening NPH (mean difference, 0.10%; 95% CI, -0.08 to 0.29 and 0.13%; 95% CI, -0.07 to 0.32, respectively). Equivalence was found between both insulin detemir groups (estimated difference, -0.03%; 95% CI, -0.21 to 0.15; P value not reported).</p> <p>Secondary:</p> <p>At 20 weeks, evening insulin detemir had changes in FPG similar to those with evening NPH (mean difference, -0.46 mmol/L; 95% CI, -1.05 to 0.13). However, morning insulin detemir had significantly higher FPG than both evening NPH and evening insulin detemir (mean difference, 0.88 mmol/L; 95% CI, 0.31 to 1.5; P=0.003 and 1.33 mmol/L; 95% CI,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin doses titrated to achieve a pre-breakfast and pre-dinner FPG ≤ 108 mg/dL.</p> <p>Existing oral antidiabetic drug therapy was continued.</p>				<p>0.85 to 1.80; $P < 0.001$, respectively).</p> <p>Prebreakfast self monitoring of blood glucose was higher in the morning insulin detemir group in comparison to both evening groups ($P < 0.001$). However, predinner self monitoring of blood glucose was lower in the morning insulin detemir group than that of the evening detemir and evening NPH groups ($P = 0.005$ and $P < 0.001$, respectively). Both evening groups resulted in similar self monitoring of blood glucose profiles.</p> <p>When compared to evening NPH, evening insulin detemir resulted in a significant risk reduction in the rate of hypoglycemic episodes over 24 hours and confirmed nocturnal episodes ($P = 0.0019$ and $P = 0.031$, respectively). On the other hand, when comparing morning and evening detemir, the rates of hypoglycemia were statistically similar. In comparison to evening NPH, morning insulin detemir did have a significant risk reduction of 87% for confirmed nocturnal hypoglycemia ($P < 0.001$).</p>
<p>Montanana et al.¹¹¹ (2008)</p> <p>Insulin detemir SC QD</p> <p>vs</p> <p>NPH SC BID</p> <p>All patients received insulin aspart at main meals.</p> <p>Concomitant treatment with metformin was allowed.</p>	<p>PG, RCT</p> <p>Type 2 diabetics ≥ 18 years of age with HbA_{1c} 7.5 to 11.0%, BMI 25 to 40 kg/m², and receiving 2 daily doses of insulin (≥ 1 premix) ≥ 3 months</p>	<p>N=271</p> <p>26 weeks</p>	<p>Primary: Change in baseline body weight</p> <p>Secondary: Change in baseline HbA_{1c} and FPG; proportion of patients achieving HbA_{1c} $\leq 7.0\%$ without hypoglycemia, incidence of hypoglycemia, safety</p>	<p>Primary: Insulin detemir (0.4kg) resulted in significantly less weight gain compared to NPH (1.9 kg; difference, 1.5 kg; $P < 0.0001$). Increases in BMI were significantly less with insulin detemir compared to NPH (difference, 0.6 kg/m²; $P < 0.0001$).</p> <p>Secondary: There was no difference in the decrease in HbA_{1c} between the insulin detemir (8.9 to 7.8%) and NPH (8.8 to 7.8%) (P value not reported).</p> <p>There was no difference in the decrease in FPG between insulin detemir (10.0 to 8.8 mmol/L) and NPH (10.1 to 8.9 mmol/L) (P value not reported).</p> <p>The proportion of patients achieving HbA_{1c} $\leq 7.0\%$ without hypoglycemia during the last four weeks of treatment was 27% with both treatments.</p> <p>The incidence of hypoglycemia was significantly lower with insulin detemir compared to NPH (RR, 0.62 (all events) and 0.43 (nocturnal); $P < 0.0001$ for both).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Hermansen et al.¹¹² (2006)</p> <p>Insulin detemir BID</p> <p>vs</p> <p>NPH insulin BID</p> <p>Basal insulin doses were adjusted to achieve pre-breakfast FBG of 108 mg/dL.</p> <p>Existing oral antidiabetic drug therapy was continued.</p>	<p>MC, OL, PG, RCT</p> <p>Adult type 2 diabetes patients with no history of insulin use, baseline HbA_{1c} 8.61% for participants taking insulin detemir and 8.51% for those randomized into the NPH group</p>	<p>N=476</p> <p>26 weeks</p>	<p>Primary: Effect on HbA_{1c}</p> <p>Secondary: FPG, proportion of participants achieving an HbA_{1c} ≤7.0%, proportion of participants achieving an HbA_{1c} ≤7.0% without hypoglycemia, 10-point self monitoring of blood glucose, frequency of hypoglycemia, and weight gain</p>	<p>Both treatments were well tolerated with no major safety concerns noted and a similar incidence of adverse events with both treatments.</p> <p>Primary: After 26 weeks, HbA_{1c} reductions in the insulin detemir group (-1.8%; P=0.004) did not differ significantly from reductions observed in the NPH group (-1.9%; P=NS).</p> <p>Secondary: After 26 weeks, the difference in mean FPG reductions between insulin detemir and NPH was not significant (0.32 mmol/L; P>0.05).</p> <p>The proportion of patients achieving an HbA_{1c} ≤7.0% was 70% in those taking insulin detemir and 74% with those taking NPH. The difference between treatment groups was not significant.</p> <p>The proportion of patients achieving an HbA_{1c} ≤7.0% without hypoglycemia was significantly higher in those taking insulin detemir (26%) compared to those taking NPH (16%; P=0.008).</p> <p>There was significantly less day-to-day fluctuation of fasting self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P=0.021).</p> <p>There were no significant differences in mean 10-point self monitoring of blood glucose profiles between the two treatment groups (P=0.19).</p> <p>There was a 47% lower risk of overall hypoglycemia with insulin detemir compared to NPH (P<0.001). There was a 55% lower risk of nocturnal hypoglycemia with insulin detemir compared to NPH (P<0.001).</p> <p>After 26 weeks, body weight change from baseline was significantly lower with insulin detemir (1.2 kg) compared to NPH (2.8 kg; P<0.001).</p>
<p>Riddle et al.¹¹³</p> <p>EDITION 1</p> <p>(2014)</p>	<p>MC, OL, PG</p> <p>Patients ≥18 years of age with a</p>	<p>N=804</p> <p>6 months</p>	<p>Primary: HbA_{1c} change from baseline at month six</p>	<p>Primary: Mean HbA_{1c} decreased similarly in the two treatment groups with a final HbA_{1c} of 7.25% (SD 0.85) in the U-300 group compared to 7.28% (0.92) in the U-100 group. The LS mean change was 0.83% for both groups;</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin glargine U-300 via modified SoloSTAR[®] pen QPM</p> <p>vs</p> <p>insulin glargine U-100 via SoloSTAR[®] pen QPM</p> <p>Dose adjustment weekly, but no more often than every three days. Metformin was continued at prior dosage throughout the study.</p>	<p>diagnosis of T2DM, HbA_{1c} 7.0 to 10.0%, and use of basal insulin therapy (≥42 units/day) with or without metformin for at least one year</p>		<p>Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events</p>	<p>difference 0.00% (95% CI, 0.11 to 0.11). Because the upper CI limit was below the 0.4% threshold, U-300 met the non-inferiority criterion.</p> <p>Secondary: Similar reductions to HbA_{1c} were observed for FPG in both treatment groups (from 8.72 mmol/L [SD 2.83] to 7.24 mmol/L [2.57] with U-300 and 8.90 mmol/L [2.94] to 7.21 mmol/L [2.40] with U-100).</p> <p>The percentages of participants attaining target HbA_{1c} levels were similar with U-300 and U-100 (39.6 and 40.9% for HbA_{1c} <7.0%, 21.0 and 21.6% for HbA_{1c} ≤6.5%, 46.3 and 44.9% for FPG ≤6.7, and 26.5 and 23.2% for FPG <5.6 mmol/L, respectively).</p> <p>Daily basal insulin dosage increased for both U-300 and U-100 at the end of the six month study. The dose increase was higher with U-300 than with U-100; LS mean difference was 0.09 units/kg/day (95% CI, 0.062 to 0.124). Mealtime insulin doses increased slightly in the first two weeks but were unchanged from baseline and alike in the two groups thereafter.</p> <p>Body weight increased by 0.9 kg in both treatment groups.</p> <p>The SMPG profiles declined in both treatment groups. No significant differences between changes in means at individual time points were demonstrated. The reduction of preinjection SMPG (combination of pre- and post-dinner measurements) from baseline to month six was similar between treatments. There was also no between-treatment difference in the change of day-to-day variability of preinjection SMPG during treatment.</p> <p>The proportion of participants with one or more confirmed or severe nocturnal hypoglycemic events between the start of week nine and month six was 36% (146/404) on U-300, compared with 46% (184/400) on U-100. Analysis of this prespecified main measure of hypoglycemia demonstrated superiority of U-300 over U-100 with a significantly lower relative risk (RR 0.79; 95% CI, 0.67 to 0.93; P=0.0045). The percentage of participants reporting severe hypoglycemia at any time was similar for the two groups with 5.0% for U-300 compared with 5.7% for U-100 (RR 0.87; 95% CI, 0.48 to 1.55).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Yki-Järvinen et al.¹¹⁴ EDITION 2 (2014)</p> <p>Insulin glargine U-300 via modified SoloSTAR[®] pen QPM</p> <p>vs</p> <p>insulin glargine U-100 via SoloSTAR[®] pen QPM</p> <p>Insulin dose adjustment weekly. Other oral antidiabetic agents were continued.</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥18 years of age with a diagnosis of T2DM, HbA_{1c} 7.0 to 10.0%, use of basal insulin therapy (≥42 units/day)</p>	<p>N=808</p> <p>6 months</p>	<p>Primary: HbA_{1c} change from baseline at month six or last visit on treatment without rescue therapy</p> <p>Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month</p>	<p>The most common adverse events were infections, gastrointestinal events, or musculoskeletal complaints; these were equally distributed between the groups.</p> <p>Primary: Mean HbA_{1c} decreased similarly in the two treatment groups with a final HbA_{1c} at six months of 7.57% for U-300 and 7.56% for U-100, representing a mean treatment difference of -0.01% (95% CI, -0.14 to 0.12). Because the upper CI limit was below the 0.4% threshold, U-300 met the non-inferiority criterion.</p> <p>Secondary: Similar reductions in FPG from baseline (-1.14 and -1.06), percentage of participants attaining HbA_{1c} <7.0% (30.6% and 30.4%) and ≤6.5% (14.5% and 14.8%), were observed in the U-300 and U-100 groups respectively. Numerically, percentage of participants attaining a FPG ≤6.7 mmol/L (48.7% and 54.1%) and <5.6 mmol/L (29.4% and 33.6%) were higher for the U-300 group than U-100 group, the difference was not statistically significant.</p> <p>Overall, glucose measurements of the 8-point profile showed a comparable decrease in SMPG for both the U-300 and U-100 groups. However, the mean prebreakfast SMPG was lower with U-100 than with U-300 during the first eight weeks, and a more gradual decrease in prebreakfast SMPG was observed with U-300 than with U-100. At month six, a similar average prebreakfast SMPG was reached in both groups (119 mg/dL for U-300 and 113 mg/dL for U-100). Comparable results were observed between U-300 and U-100 for change in preinjection SMPG and variability in preinjection SMPG.</p> <p>The daily basal insulin dose increased from baseline to month six in both groups, mainly during the first 12 weeks. There was a significant difference in insulin dose between treatment groups at month six, with a LS mean difference of 11 units/day (95% CI, 8 to 14), with those in the U-300 group requiring 10% more basal insulin (units/kg/day) than those receiving U-100.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			six, and other adverse events	<p>Overall, 123 participants (30.5%) in the U-300 group experienced 379 nocturnal hypoglycemic events, and 169 participants (41.6%) in the U-100 group experienced 766 nocturnal hypoglycemic events. A significantly lower percentage of participants reported at least one nocturnal or severe hypoglycemic event from week nine to month six with U-300 (21.6%) compared with U-100 (27.9%). Analysis of this prespecified main secondary end point demonstrated superiority of U-300 over U-100 (RR, 0.77; 95% CI, 0.61 to 0.99, P=0.038). . The risk of nocturnal confirmed or severe hypoglycemia was also reduced with U-300 compared with U-100 during the six-month study period (RR, 0.71; 95% CI, 0.58 to 0.86).</p> <p>During the six-month treatment period, 288 participants (71.5%) treated with U-300 and 322 participants (79.3%) treated with U-100 reported one or more hypoglycemic events. In total, 2,750 hypoglycemic events were reported in the U-300 group and 3,675 in the U-100 group.</p> <p>The most common adverse events in the U-300 and U-100 groups were infections, nervous system disorders, gastrointestinal events and musculoskeletal complaints. These were equally distributed between the treatment groups.</p>
<p>Bolli et al.¹¹⁵ EDITION 3 (2015)</p> <p>Insulin glargine U-300 via TactiPen® injector QPM</p> <p>vs</p> <p>insulin glargine U-100 via SoloSTAR® pen QPM</p> <p>Insulin dose adjustment weekly.</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥18 years of age with a diagnosis of T2DM for at least one year, use of oral glucose-lowering drugs in the last six months, and insulin naïve</p>	<p>N=873</p> <p>6 months</p>	<p>Primary: HbA_{1c} change from baseline at month six</p> <p>Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin</p>	<p>Primary: The mean decrease in HbA_{1c} was equivalent in the two treatment groups. At month six, the LS mean difference in change of HbA_{1c} was 0.04% (95% CI, -0.09 to 0.17) meeting the non-inferiority criterion.</p> <p>Secondary: The proportion of participants reaching target HbA_{1c} or laboratory-measured FPG at month six was much the same in the two treatment groups.</p> <p>Similar results in both the U-300 and U-100 groups were observed for change in pre-injection SMPG and variability in pre-injection SMPG. FPG from baseline to month six was somewhat greater in the U-100 group than in the U-300 group (LS mean difference, 0.39; 95% CI, 0.10 to 0.68). Over the 24-hour period, the eight-point SMPG profiles showed a similar decrease from baseline to month six with both U-300 and U-100 (LS mean difference, 0.18; 95% CI, -0.07 to 0.42). The pre-breakfast SMPG</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events</p>	<p>decreased more gradually with U-300 than with U-100.</p> <p>The basal insulin dose increased throughout the six-month treatment period in both treatment groups, but more so with U-300; mean increase was 0.62 (0.29) U/kg/day U-300, and to 0.53 (0.24) U/kg/day with U-100 (no P value reported).</p> <p>Between the start of week nine and month six, the percentage of participants experiencing at least one nocturnal confirmed or severe hypoglycemic event was 16% with U-300 and 17% with U-100 (RR, 0.89; 95% CI, 0.66 to 1.20). The percentage of participants who experienced ≥ 1 confirmed or severe hypoglycemic event was lower with U-300 (201/435, 46%) than with U-100 (230/438, 53%) over the six-month study period (RR, 0.88; 95% CI, 0.77 to 1.01).</p> <p>Weight gain during the treatment period was lower with U-300 (LS mean increase, 0.49; 95% CI, 0.14 to 0.83 kg) than with U-100 (LS mean increase 0.71; 95% CI, 0.36 to 1.06 kg; P value was non-significant).</p>
<p>Ritzel et al.¹¹⁶ (2015)</p> <p>Insulin glargine U-300 via pen injector QPM</p> <p>vs</p> <p>insulin glargine U-100 via SoloSTAR[®] pen QPM</p> <p>Insulin dose adjustment weekly.</p>	<p>MA of EDITION 1, 2, and 3</p> <p>Patients ≥ 18 years of age with a diagnosis of T2DM</p>	<p>N=2496</p> <p>6 months</p>	<p>Primary:</p> <p>Change in HbA_{1c} from baseline, proportion of participants with HbA_{1c} <7.0, change in average pre-injection SMPG from baseline, and change in laboratory-measured FPG from baseline</p> <p>Secondary:</p> <p>Safety and tolerability</p>	<p>Primary:</p> <p>The mean decrease in HbA_{1c} was similar in the two treatment groups. The proportion of participants who reached target HbA_{1c} after 6 months of treatment was similar in both treatment groups: 449 participants (36.2%) on U-300 and 438 participants (35.5%) on U-100. Laboratory-measured FPG decreased similarly in both groups. There was also no between-treatment difference in the variability of pre-injection SMPG at month six.</p> <p>Secondary:</p> <p>The annualized rate (events per participant-year) of confirmed (≤ 70 mg/dl) or severe hypoglycemia at any time of day over the six-month study period was 15.22 with U-300 and 17.73 with U-100 (rate ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.0116), corresponding to a relative difference of 14% in favor of U-300.</p> <p>No between-treatment differences in safety profile were identified, with similar rates of adverse events reported across all three studies.</p>
<p>Strojek et al.¹¹⁷</p>	<p>MC, NI, OL, PG,</p>	<p>N=433</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2009)</p> <p>Insulin glargine QD</p> <p>vs</p> <p>biphasic aspart 30 QD</p> <p>Insulin doses were titrated to achieve a FPG of 5.0 to 6.1 mmol/L.</p> <p>All patients also received metformin and glimepiride.</p>	<p>RCT</p> <p>Patients ≥18 years of age with type 2 diabetes who were insulin-naïve and receiving oral diabetes medications for ≥6 months, with HbA_{1c} >7.0 and ≤11.0%, BMI ≤40 kg/m²</p>	<p>26 weeks</p>	<p>HbA_{1c} at 26 weeks</p> <p>Secondary: Proportion of patients achieving HbA_{1c} ≤6.5 and <7.0% without hypoglycemia after 26 weeks, HbA_{1c} reduction by >1% from baseline, nine-point self-measured plasma glucose profiles, PPG increments, Diab-MedSat and safety</p>	<p>HbA_{1c} at 26 weeks was 7.1 and 7.3% with biphasic aspart and insulin glargine, respectively (difference, -0.16%, 95% CI, -0.30 to -0.02; <i>P</i>=0.029), demonstrating non-inferiority.</p> <p>Secondary: In both treatment groups, 25% of patients achieved HbA_{1c} ≤6.5%.</p> <p>In the biphasic aspart group, 44.9% of patients achieved HbA_{1c} <7.0%, and 19.4% of patients achieved this value without hypoglycemia. The corresponding results with insulin glargine were 44.9 and 20.0%, respectively (<i>P</i> values not reported).</p> <p>In the biphasic aspart and insulin glargine groups, 60 and 57% of patients, respectively, achieved HbA_{1c} reduction by >1% (<i>P</i> value not reported).</p> <p>Biphasic aspart was associated with lower post-dinner and bedtime plasma glucose compared to insulin glargine on the nine-point self-measured plasma glucose profiles (<i>P</i><0.05). No significant differences were observed at other time points.</p> <p>PPG increments were comparable between the two groups.</p> <p>No significant difference was seen between biphasic aspart and insulin glargine in treatment satisfaction as measured by Diab-MedSat questionnaire (score difference, -0.11; 95% CI, -2.36 to 2.14; <i>P</i> value not reported).</p> <p>Fifty-eight and 51% of patients in the biphasic aspart and insulin glargine groups, respectively, reported at least one hypoglycemic event (RR, 1.41; 95% CI, 1.03 to 1.93; <i>P</i>=0.034). The risk of nocturnal hypoglycemia was also higher with biphasic aspart compared to insulin glargine (RR, 2.41; 95% CI, 1.34 to 4.34; <i>P</i>=0.003). No significant differences were seen in daytime hypoglycemia.</p> <p>Treatment-emergent adverse events were reported in 51 and 48% of patients in the biphasic aspart and insulin glargine groups, respectively.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Less than 1% of patients reported serious adverse events that are possibly or probably related to study medications. One treatment-emergent death was reported in the insulin glargine group and was considered not related to the study medication. No significant differences were seen in cardiovascular risk markers, waist circumference or body weight.</p>
<p>Bretzel et al.¹¹⁸ (2008) APOLLO</p> <p>Insulin glargine QD vs pre meal insulin lispro</p> <p>Insulin glargine doses were titrated to achieve FPG <5.5 mmol/L.</p> <p>Insulin lispro doses were titrated to achieve pre-prandial glucose <5.5 mmol/L and PPG <7.5 mmol/L.</p> <p>The dose of oral diabetes medications remained stable throughout the entire study.</p>	<p>MC, NI, OL, PG, RCT</p> <p>Patients 18 to 75 years of age with type 2 diabetes for ≥1 year, HbA_{1c} 7.5 to 10.5%, BMI ≤35 kg/m², FPG ≥6.7 mmol/L and receiving oral diabetes medications for ≥6 months with no dose change in the past 3 months</p>	<p>N=418 (intent-to-treat)</p> <p>N=377 (per-protocol)</p> <p>44 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline at 44 weeks</p> <p>Secondary: Proportion of patients with HbA_{1c} ≤6.5 or ≤7.0%, change in FPG, proportion of patients with FPG ≤5.5 mmol/L, changes in nocturnal blood glucose and eight-point blood glucose profiles, percentage of patients with nocturnal, severe and symptomatic hypoglycemia</p>	<p>Per-protocol population was used in all efficacy endpoint analyses for non-inferiority testing. Intent-to-treat population was used subsequently for superiority testing.</p> <p>Primary: The adjusted mean change in HbA_{1c} was -1.71 and -1.87% with insulin glargine and insulin lispro, respectively, which met the predefined 0.4% limit for non-inferiority between the two groups. Intent-to-treat analysis failed to show superiority (-1.69 vs -1.82%; <i>P</i>=0.0908).</p> <p>Secondary: Thirty percent and 38% of patients reached HbA_{1c} ≤6.5% and 57 and 69% of patients reached HbA_{1c} ≤7.0% in the insulin glargine and insulin lispro groups, respectively (<i>P</i> values not reported).</p> <p>Change in FPG from baseline at 44 weeks was -4.3±2.3 and -1.8±2.3 mmol/L with insulin glargine and insulin lispro (<i>P</i><0.0001). Significantly more patients in the glargine group achieved FPG ≤5.5 mmol/L compared to the insulin lispro group (38 vs 6%; <i>P</i> value not reported [per-protocol]; 35 vs 5%; <i>P</i><0.001 [intent-to-treat]).</p> <p>Decrease in nocturnal glucose was significantly greater with insulin glargine compared to insulin lispro (-3.3 vs -2.6 mmol/L; <i>P</i>=0.0041 [per-protocol]; -3.3 vs -2.7 mmol/L; <i>P</i>=0.0017 [intent-to-treat]).</p> <p>A greater reduction was seen with insulin lispro compared to insulin glargine in PPG after breakfast, lunch, dinner and bedtime (<i>P</i><0.05 for all).</p> <p>The rate of nocturnal hypoglycemia per patient was similar between insulin glargine and insulin lispro (0.42 vs 0.27; <i>P</i>=0.0709). The rates of severe and symptomatic hypoglycemia are significantly lower with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Patients who were treated with a sulfonylurea were converted to equivalent dose of glimepiride during the screening phase.</p>				<p>insulin glargine compared to insulin lispro (0.02 vs 0.06; $P=0.0989$; 3.46 vs 11.02; $P<0.0001$, respectively).</p>
<p>Buse et al.¹¹⁹ (2009) DURABLE Insulin glargine SC QD vs biphasic lispro 25 SC BID</p>	<p>MC, OL, PG, RCT Type 2 diabetics 30 to 80 years of age with HbA_{1c} >7.0%, receiving ≥2 oral antidiabetic agents for 90 days, and BMI <45 kg/m²</p>	<p>N=1,045 24 weeks</p>	<p>Primary: HbA_{1c} at trial end Secondary: Change in baseline HbA_{1c}, body weight, and insulin dose; proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%; seven-point self-monitored glucose profiles; incidence of hypoglycemia; safety</p>	<p>Primary: Biphasic lispro 25 achieved a significantly lower final HbA_{1c} compared to insulin glargine (7.3 vs 7.2%; $P=0.005$).</p> <p>Secondary: Biphasic lispro 25 had significantly greater decreases in HbA_{1c} compared to insulin glargine (-1.7 vs -1.8%; $P=0.005$).</p> <p>Biphasic lispro 25 was associated with significantly more weight gain compared to insulin glargine (2.5 vs 3.6 kg; $P<0.0001$).</p> <p>After 24 weeks, the total daily insulin dose was significantly higher with biphasic lispro 25 compared to insulin glargine (0.40 vs 0.47 units/kg; $P<0.001$).</p> <p>The proportion of patients achieving HbA_{1c} <7.0% was significantly greater with biphasic lispro 25 compared to insulin glargine (40.3 vs 47.5%; $P<0.001$). There was no difference between the two treatments in the proportions of patients achieving HbA_{1c} ≤6.5% (22.2 vs 24.6%; $P=0.174$).</p> <p>Biphasic lispro 25 had a significantly higher rate of overall hypoglycemia (23.1 vs 28.0 episodes per patient-year; $P=0.007$), but a significantly lower rate of nocturnal hypoglycemia compared to insulin glargine (11.4 vs 8.9 episodes per patient year $P=0.009$). The rate of severe hypoglycemia was similar between the two treatments (0.03 vs 0.10 episodes per patient year; $P=0.167$).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Overall, 4.3 and 6.2% of patients receiving insulin glargine and biphasic lispro 25 experienced at least one serious adverse event (P=0.051); the rate of cardiovascular-related serious adverse events was similar between the two treatments (26 vs 29%; P=0.716). There were six and 15 adverse events leading to discontinuation with insulin glargine and biphasic lispro 25 (P=0.077). One and five deaths occurred with insulin glargine and biphasic lispro 25 (P=0.218).</p>
<p>Yki-Järvinen et al.¹²⁰ (2000)</p> <p>Insulin glargine HS vs NPH insulin HS</p> <p>Initial doses were titrated to achieve FPG target ≤ 120 mg/dL.</p> <p>Existing oral antidiabetic drug therapy was continued.</p>	<p>RCT</p> <p>Patients 40 to 80 years of age with type 2 diabetes for at least 3 years, BMI < 40 kg/m², HbA_{1c} 7.5 to 12.0%, previous oral therapy with either sulfonylureas alone or combined with acarbose, metformin, or metformin alone for at least 1 year, negative history of ketoacidosis, women of childbearing potential were required to be on contraceptive protection, willingness to perform self monitoring of blood glucose</p>	<p>N=426</p> <p>52 weeks</p>	<p>Primary: HbA_{1c}</p> <p>Secondary: FPG, 24-hour blood glucose profile, incidence of hypoglycemia, and serum C-peptide concentrations</p>	<p>Primary: The HbA_{1c} in the insulin glargine group decreased to 8.34\pm0.09% at end point from baseline (P<0.001) and 8.24\pm0.09% in the NPH group (P<0.001).</p> <p>Secondary: In the group of patients that achieved target FPG ≤ 120 mg/dL, HbA_{1c} decreased to 7.75\pm0.14% and 7.60\pm0.12% in the insulin glargine and NPH groups, respectively. However, there was no difference between groups (P values not reported).</p> <p>At study end point, blood glucose concentrations were significantly lower in the insulin glargine group than the NPH group before and after dinner. However, in the group of patients that achieved target FPG, blood glucose at 3 AM was significantly lower in patients taking NPH than those taking insulin glargine (P=0.0012).</p> <p>In the entire group of patients, the percentage of patients experiencing at least one symptomatic hypoglycemic episode was lower in the insulin glargine group than the NPH group. In the group of patients achieving target FPG, the percentage of patients experiencing symptomatic hypoglycemia was 33.0% and 50.7% in the insulin glargine and NPH groups, respectively (P=0.027).</p> <p>Serum C-peptide concentrations decreased similarly from baseline in both treatment groups (P<0.001).</p>
<p>Riddle et al.¹²¹ (2003)</p>	<p>CS, MC, OL, PG, RCT</p>	<p>N=764</p> <p>24 weeks</p>	<p>Primary: Percentage of patients achieving</p>	<p>Primary: The percentage of patients reaching a target HbA_{1c} $\leq 7.0\%$ without a single instance of symptomatic nocturnal hypoglycemia was achieved by more</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin glargine HS vs NPH insulin HS</p> <p>Insulin doses were titrated to achieve target FPG ≤ 100 mg/dL.</p> <p>Existing oral antidiabetic drug therapy was continued.</p>	<p>Patients 30 to 70 years of age with type 2 diabetes for ≥ 2 years, treated with stable doses of 1 or 2 oral antidiabetic drug for ≥ 3 months, BMI 26 to 40 kg/m², HbA_{1c} 7.5 to 10.0%, FPG ≥ 140 mg/dL at screening</p>		<p>an HbA_{1c} $\leq 7.0\%$ without a single instance of symptomatic nocturnal hypoglycemia confirmed by plasma-referenced glucose ≤ 72 mg/dL</p> <p>Secondary: Changes from baseline in HbA_{1c}, FPG, and weight; percentage of patients achieving an HbA_{1c} $\leq 7.0\%$ or FPG ≤ 100 mg/dL independent of the occurrence of hypoglycemia; percentage of patients achieving FPG ≤ 100 mg/dL without confirmed hypoglycemia; overall rates of symptomatic hypoglycemia</p>	<p>patients taking insulin glargine than patients taking NPH (32.2 vs 26.7%, respectively; P<0.05).</p> <p>Secondary: Mean HbA_{1c} at end point was 6.96% with insulin glargine and 6.97% with NPH (between-treatment difference, -0.03%; 95% CI, -0.13 to 0.08; P=NS). Both groups also achieved comparable decreases in FPG at end point (between-treatment difference, -3.6 mg/dL; 95% CI, -8.82 to 1.62; P=NS). Weight increased similarly from baseline to end point in both groups (between-treatment difference, 0.2 kg; 95% CI, -0.24 to 0.68; P=NS).</p> <p>The HbA_{1c} $\leq 7.0\%$ target was reached by 58.0% of patients on insulin glargine and 57.3% of patients in the NPH group.</p> <p>The goal FPG ≤ 100 mg/dL was achieved by 36.2% of patients on insulin glargine and 34.4% of patients on NPH. This target was achieved without hypoglycemia more often by patients taking insulin glargine. FPG ≤ 100 mg/dL without documented nocturnal hypoglycemia was achieved by 22.1% of patients taking insulin glargine compared to 15.9% of patients taking NPH (P<0.03).</p> <p>The rates of hypoglycemia (events/patient-year) with insulin glargine vs NPH were 13.9 vs 17.7, respectively for all symptomatic events (P<0.02) and 9.2 vs 12.9, respectively, for all confirmed events (P<0.005).</p>
<p>Rosenstock et al.¹²² (2009)</p> <p>Insulin glargine HS</p>	<p>MC, OL, PG, RCT</p> <p>Patients 30 to 70 years of age with</p>	<p>N=1,017</p> <p>5 years</p>	<p>Primary: Percentage of patients with three or more step</p>	<p>Primary: In the ITT analysis, 12.5% of patients in the insulin glargine group experienced a ≥ 3 step progression in Early Treatment Diabetic Retinopathy Study score after five years compared to 14.6% of patients receiving NPH</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>NPH insulin BID</p> <p>Insulin doses were titrated to achieve FPG \leq120 mg/dL during the first 3 years of the study, then FPG \leq100 mg/dL during the last 2 years of the study.</p> <p>Oral antidiabetic drug and/or prandial insulin could be continued or modified during the trial, and regular insulin could be added with meals at the investigator's discretion.</p>	<p>type 2 diabetes with HbA_{1c} 6.0 to 12.0% who were treated with oral antidiabetic drugs or insulin (alone or in combination) for \geq1 year</p>		<p>progression in Early Treatment Diabetic Retinopathy Study score after five years of treatment with either insulin glargine or NPH insulin</p> <p>Secondary: HbA_{1c}, FPG, and hypoglycemia</p>	<p>insulin (difference, -2.10%; 95% CI, -6.29 to 2.09). In the PP analysis, 14.2 and 15.7% of patients experienced a \geq3 step progression in Early Treatment Diabetic Retinopathy Study score after five years, respectively (difference, -1.98%; 95% CI, -7.02 to 3.06).</p> <p>Secondary: After five years, the mean FPG in the insulin glargine group was 7.8 and 7.7 mmol/L in the NPH insulin group (ITT population).</p> <p>The proportion of patients achieving FPG \leq5.6 mmol/L was 28.5% with insulin glargine and 24.3% with NPH insulin.</p> <p>After five years, the mean HbA_{1c} (last observation carried forward) improved from a baseline of 8.4 and 8.3 to 7.8 and 7.6% for patients in the insulin glargine and NPH insulin groups, respectively (difference, 0.21%; P=0.0053).</p> <p>Weight gain was 3.7 kg with insulin glargine compared to 4.8 kg with NPH insulin (ITT; P=0.0505).</p> <p>The use of NPH insulin was associated with a greater incidence of severe hypoglycemia than insulin glargine (11.1 vs 7.6%, respectively; P=0.0439). However, there was no significant difference in symptomatic hypoglycemia (P=0.1366) or nocturnal hypoglycemia (P=0.2248) between the treatment groups.</p>
<p>Aschner et al.¹²³ (2015) GALAPAGOS</p> <p>Insulin glargine (\pm glulisine)</p> <p>vs</p> <p>premixed insulin (insulin aspart 30% and protamine-</p>	<p>MC, OL, RCT</p> <p>Insulin-naïve type 2 diabetes patients \geq35 years of age failing oral agents (HbA_{1c} 7.0 to 10.5%)</p>	<p>N=923</p> <p>24 weeks</p>	<p>Primary: Percentage of patients reaching HbA_{1c} < 7% at study end without any documented symptomatic hypoglycemia (blood glucose \leq3.1 mmol/L)</p> <p>Secondary:</p>	<p>Primary: A similar percentage of patients treated with glargine (\pm glulisine) (33.2%) or premix (31.4%) achieved HbA_{1c} <7% with no documented symptomatic hypoglycemia over the 24-week treatment period. The glargine (\pm glulisine) strategy did not show superiority compared with a premix strategy on the primary endpoint (difference in success rate = 1.8%; P=0.56). The primary endpoint was met by 43.8% of those treated with glargine alone, 19.3% treated with glargine + glulisine, and 37.7% and 27.9% of those treated with once-daily and twice-daily premix, respectively.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>crystallized insulin aspart (70%)</p> <p>continuing metformin ± insulin secretagogue</p>			<p>Changes in HbA_{1c}, percentage of patients who achieved HbA_{1c} <7% and <6.5%, weight, insulin dose, hypoglycemia, adverse events</p>	<p>Mean HbA_{1c} values were the same at baseline in both groups (8.7%), decreased throughout the study, and were 7.2% with glargine (± glulisine) and 7.0% with premix at study end. The least squares (LS) mean change (standard error) from baseline to study end was -1.48 (0.04) % and -1.64 (0.04) % with glargine (± glulisine) and premix, respectively. The LS mean difference between groups was 0.16% (95% CI, 0.04 to 0.27) in favor of premix (P=0.008). The LS mean change from baseline in FPG was greater with glargine (± glulisine) (-3.0 mmol/l) than with premix (-2.6 mmol/l), with an LS mean difference of -0.3 mmol/l (95% CI, -0.5 to -0.2; P<0.001). A similar percentage of patients treated with glargine (± glulisine) or premix experienced at least one treatment-emergent adverse event (34.6 vs 35.7%). Mean body weight gain was similar for glargine (± glulisine) and premix. More patients using premix achieved target (52.6 vs 43.2%, P=0.005); symptomatic hypoglycemia was less with glargine (1.17 vs 2.93 events/patient-year).</p>
<p>Fritsche et al.¹²⁴ (2003)</p> <p>Insulin glargine AM and glimepiride 3 mg QD</p> <p>vs</p> <p>insulin glargine HS and glimepiride 3 mg QD</p> <p>vs</p> <p>NPH insulin HS and glimepiride 3 mg QD</p>	<p>MC, OL, PG, RCT</p> <p>Patients with type 2 diabetes <75 years of age, previously on oral therapy with any sulfonylurea as monotherapy or in combination with metformin or acarbose, BMI <35 kg/m², FPG ≥120 mg/dL, HbA_{1c} 7.5 to 10.5%</p>	<p>N=700</p> <p>28 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to end point, frequency of patients who experienced hypoglycemic episodes during the study</p> <p>Secondary: HbA_{1c} ≤7.5%, FBG ≤100 mg/dL, response rates, mean 24-hour blood glucose values, hypoglycemic events and adverse events</p>	<p>Primary: Over the 24-week treatment period, HbA_{1c} levels improved by -1.24% (two-sided 90% CI, -1.10 to -1.38) with morning insulin glargine, -0.96% (90% CI, -0.81 to -1.10) with bedtime insulin glargine and -0.84% (90% CI, -0.69 to -0.98) with bedtime NPH (P values not reported).</p> <p>Improvement in HbA_{1c} was significant in patients receiving morning insulin glargine than in patients receiving NPH (-0.40%; 90% CI, -0.23 to -0.58; P<0.001) and bedtime insulin glargine (-0.28%; 90% CI, -0.11 to -0.46; P=0.008).</p> <p>Secondary: More patients in the morning insulin glargine group achieved HbA_{1c} level of <7.5% (43%) than patients in the bedtime NPH (32%) and bedtime insulin glargine groups (33%; P=0.021).</p> <p>FPG levels improved in all three groups. The average reduction in FPG level achieved over the 24-week treatment did not differ among the groups (P>0.2).</p> <p>The morning insulin glargine group showed a greater decrease in mean daily blood glucose levels compared to both the bedtime NPH group</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>(P<0.001) and the bedtime insulin glargine group (P=0.002).</p> <p>Hypoglycemic events were similar among the three groups. The number of patients experiencing nocturnal hypoglycemia was lower in both the morning and bedtime insulin glargine groups than with the bedtime NPH group (P<0.001). Fewer patients experienced symptomatic hypoglycemia with bedtime insulin glargine (43%) than with bedtime NPH (58%; P=0.001) and morning insulin glargine (56%; P=0.004).</p> <p>Adverse event rates were similar in all three groups (P values not reported).</p>
<p>Pan et al.¹²⁵ (2007)</p> <p>Insulin glargine HS and glimepiride 3 mg QD</p> <p>vs</p> <p>NPH insulin HS and glimepiride 3 mg QD</p>	<p>MN, NI, OL, PG, RCT</p> <p>Insulin-naïve Asian patients 40 to 80 years of age with type 2 diabetes and random venous plasma glucose concentration ≥ 11.1 mmol/L, FPG ≥ 7 mmol/L, or PPG ≥ 11.1 mmol/L 2 hours after oral glucose tolerance test, poorly controlled on oral antidiabetic drug for ≥ 3 months prior to study entry, BMI 20 to 35 kg/m², HbA_{1c} 7.5 to 10.5%, and FPG >120 mg/dL</p>	<p>N=448</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to endpoint</p> <p>Secondary: Mean FPG level, eight-point blood glucose profiles, proportion of patients with HbA_{1c} <7.5%, proportion of combined responders (defined as HbA_{1c} <7.5% and FPG ≤ 120 mg/dL), change in BMI, hypoglycemia</p>	<p>Primary: The insulin glargine group had a decrease of -1.10% in HbA_{1c} vs -0.92% in the NPH group. There was not a statistically significant difference between both groups (P=0.0631). The results were confirmed in a full analysis set, the difference between adjusted mean changes in the two groups was 0.22 (95% CI, 0.02 to 0.42; P=0.0319).</p> <p>Secondary: FPG decreased to a similar extent in both the insulin glargine and NPH groups (-106 and -104 mg/dL, respectively; P value not reported).</p> <p>At study end, the eight-point blood glucose profiles were similar in both the insulin glargine and NPH groups, except at postdinner time, when the use of insulin glargine resulted in lower glucose concentrations (P=0.0436). The insulin glargine group had greater decreases in daily blood glucose levels than the NPH group (-94 vs -80 mg/dL, respectively; P=0.018).</p> <p>The proportion of patients achieving HbA_{1c} <7.5% at the end of the study was greater for the insulin glargine group than the NPH group (38.1 vs 30.3%, respectively). This was also consistent with the proportion of patients achieving target FPG (62.3 vs 58.7%, respectively). In the insulin glargine group, a greater proportion of patients achieved HbA_{1c} <7.5% without experiencing nocturnal symptomatic hypoglycemia (P=0.0174).</p> <p>Both groups had similar changes in BMI from baseline (1.40 and 1.29 kg/m² in the insulin glargine and NPH groups, respectively).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The number of hypoglycemic episodes was significantly lower with insulin glargine than with NPH (P<0.004). These differences were seen in particular with symptomatic hypoglycemia (P<0.0003), severe hypoglycemia (P<0.03), and nocturnal hypoglycemia (P<0.001).
Eliaschewitz et al. ¹²⁶ (2006) Insulin glargine HS and glimepiride 4 mg QD vs NPH insulin HS and glimepiride 4 mg QD Insulin doses were titrated to achieve target FPG ≤100 mg/dL.	MC, OL, RCT Men and women ≤75 years of age with type 2 diabetes, who had not achieved good metabolic control on oral antidiabetic drugs for at least 6 months, with HbA _{1c} levels 7.5 to 10.5%, FPG ≥100 mg/dL, and BMI ≤35 kg/m ²	N=528 24 weeks	Primary: Change in HbA _{1c} from baseline to end of study Secondary: Percentage of patients who responded to treatment (defined as those who achieved HbA _{1c} ≤7.5% and FPG ≤100 mg/dL by end of study), change in FPG from baseline, hypoglycemia	Primary: At 24 weeks, both groups demonstrated equivalence in change in HbA _{1c} (adjusted mean difference, -0.047; 90% CI, -0.232 to 0.138). Based on equivalence result, an analysis was conducted and also revealed no significant difference between groups (adjusted mean difference, -0.029; 90% CI, -0.210 to 0.153; P=0.795). Secondary: The percentages of responders were similar in both the insulin glargine group and NPH group for HbA _{1c} ≤7.5% (50.4 vs 48.0%, respectively; P=0.529) and FPG ≤100 mg/dL (42.1 vs 39.8%, respectively; P=0.752). There was no significant difference between groups in changes in FPG (P=0.298). The insulin glargine group had a lower RR of hypoglycemia than the NPH group (RR, 1.27; 95% CI, 1.03 to 1.57). There was also a greater reduction in the risk of nocturnal hypoglycemia (RR, 1.2; 95% CI, 1.09 to 1.37) and confirmed nocturnal events (RR, 1.19; 95% CI, 1.07 to 1.31) in the insulin glargine group than the NPH group (P value not reported).
Yki-Järvinen et al. ¹²⁷ (2006) Insulin glargine HS and metformin (G+MET) vs NPH insulin HS	MC, OL, PG, RCT Men and women 35 to 75 years of age with type 2 diabetes previously treated with a stable dose of sulfonylurea and metformin (>1.5 g) or metformin alone	N=110 36 weeks	Primary: Change in HbA _{1c} from baseline Secondary: Diurnal glucose concentrations, symptomatic hypoglycemia	Primary: At 36 weeks, HbA _{1c} decreased from 9.13±0.15% to 7.14±0.12% and from 9.26±0.15% to 7.16±0.14% in the G+MET and NPH+MET groups, respectively. The changes in HbA _{1c} were determined to be not significant between groups (P value not reported). Secondary: The diurnal profiles were consistently lower in the G+MET group compared to the NPH+MET group (8.6±0.3 vs 10.1±0.3 mmol/L, respectively; P=0.002). During the first 12 weeks, the G+MET group had significantly lower

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>and metformin (NPH+MET)</p> <p>Insulin doses were titrated to achieve an FPG 72 to 100 mg/dL in both groups.</p>	<p>for at least 3 months prior to screening, with a BMI 20 to 40 kg/m², HbA_{1c} ≥8.0%, FPG ≥7 mmol/L measured during self monitoring of blood glucose between 4 and 2 weeks prior to study start, and fasting C-peptide ≥0.33 nmol/L</p>			<p>number of episodes of symptomatic hypoglycemia than the NPH+MET group, but the rates became similar thereafter. The frequency of hypoglycemia averaged 5.4 and 8.0 episodes/patient-year for the G+MET and NPH+MET groups, respectively (P=0.12).</p>
<p>Holman et al.¹²⁸ (2007)</p> <p>Biphasic insulin aspart 30 BID</p> <p>vs</p> <p>insulin aspart TID before meals</p> <p>vs</p> <p>insulin detemir HS to BID (AM and HS)</p> <p>Insulin doses were titrated to achieve pre-meal capillary blood glucose 72 to 99 mg/dL or PPG</p>	<p>MC, OL, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes who had not been previously treated with insulin, HbA_{1c} 7.0 to 10.0%, on maximum tolerated doses of metformin and a sulfonylurea for ≥4 months, and BMI ≤40 kg/m²</p>	<p>N=708</p> <p>1 year</p>	<p>Primary: HbA_{1c} at one year</p> <p>Secondary: Proportion of patients with HbA_{1c} ≤6.5%, proportion of patients with ≤6.5% but without hypoglycemia during weeks 48 to 52, rate of hypoglycemia, weight gain, eight-point self monitoring blood glucose</p>	<p>Primary: At 52 weeks, the reduction in HbA_{1c} from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 0.8% in the basal group. The difference between the HbA_{1c} levels in the biphasic group (7.3%) and the prandial group (7.2%) were not significant (P=0.08); however, the HbA_{1c} level was higher in the basal group (7.6%; P<0.001 for both comparisons with the basal group).</p> <p>Secondary: The proportion of patients with an HbA_{1c} ≤6.5% was 17% in the biphasic group and 23.9% in the prandial group (P=0.08). The proportion of patients in the basal group was 8.1%, which was lower than the other groups (P=0.001 for the comparison with the biphasic group and P<0.001 for the comparison with the prandial group).</p> <p>The proportion of patients with an HbA_{1c} ≤6.5% without hypoglycemia during weeks 48 to 52 were 52.5, 43.9, and 78.9% in the biphasic, prandial, and basal groups, respectively (P=0.001).</p> <p>The proportion of patients with an HbA_{1c} level of ≤7.0% was significantly different between the basal group (27.8%) and each of the two other groups (biphasic group, 41.7%; prandial group, 48.7%; P<0.001 for both</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>90 to 126 mg/dL.</p> <p>Existing oral antidiabetic drug regimens were continued.</p>				<p>comparisons).</p> <p>Patients gained weight on all regimens, with a greater increase in the prandial group (5.7 kg; P<0.001 vs basal) than in the biphasic group (4.7 kg; P=0.005 vs prandial and P<0.001 vs basal) or the basal group (1.9 kg).</p> <p>There were no significant differences in overall mean self monitoring blood glucose among the treatment groups.</p> <p>Overall rates of hypoglycemia were 91.9% in the biphasic group (P=0.08 vs prandial), 96.2% in the prandial group (P<0.001 vs basal), and 73.9% in the basal group (P<0.001 vs biphasic). The mean numbers of hypoglycemic events per patient per year were 5.7 in the biphasic group, 12.0 in the prandial group, and 2.3 in the basal group.</p>
<p>Holman et al.¹²⁹ (2009)</p> <p>Biphasic insulin aspart 30 BID</p> <p>vs</p> <p>insulin aspart TID before meals</p> <p>vs</p> <p>insulin detemir HS to BID (AM and HS)</p> <p>Insulin doses were titrated to achieve pre-meal capillary blood glucose 72 to 99 mg/dL or PPG 90 to 126 mg/dL.</p>	<p>MC, OL, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes who had not been previously treated with insulin, HbA_{1c} 7.0 to 10.0%, on maximum tolerated doses of metformin and a sulfonylurea for ≥4 months, and BMI ≤40 kg/m²</p>	<p>N=708</p> <p>3 years</p>	<p>Primary: HbA_{1c} at three years</p> <p>Secondary: Proportion of patients with HbA_{1c} ≤6.5%, rate of hypoglycemia, weight gain, self monitoring blood glucose</p>	<p>Primary: The mean reduction in HbA_{1c} from baseline to year three was 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group.</p> <p>Secondary: The proportion of patients with an HbA_{1c} ≤6.5% was 31.9% in the biphasic group and 44.7% in the prandial group (P=0.006). The proportion of patients in the basal group was 43.2% (P=0.03 vs biphasic).</p> <p>The proportion of patients with an HbA_{1c} ≤7.0% was 49.4% in the biphasic group, 67.4% in the prandial group (P<0.001 vs biphasic) and 63.2% in the basal group (P=0.02 vs biphasic).</p> <p>Self monitoring blood glucose values were significantly lower in the prandial group than in the biphasic group (P=0.001), but were not significantly different than in the basal group (P=0.06). No significant differences were seen in fasting glucose values in the three groups. A greater mean reduction in postprandial glucose values was seen in the prandial group than in either the biphasic group (P<0.001) or the basal group (P=0.007), with a greater reduction in the basal group than in the biphasic group (P=0.04). The reduction in 3 a.m. glucose values was significantly greater in the basal group than in the prandial group (P=0.02)</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Existing oral antidiabetic drug regimens were continued.				<p>Patients gained weight on all regimens, with a greater increase in the prandial group (6.4 kg; P<0.001 vs basal) than in the biphasic group (5.7 kg; P=0.20 vs prandial and P=0.005 vs basal) or the basal group (3.6 kg).</p> <p>Overall rates of hypoglycemia were 49.4% in the biphasic group (P=0.68 vs prandial), 51.0% in the prandial group (P=0.14 vs basal), and 44.0% in the basal group (P=0.29 vs biphasic). The median number of hypoglycemic events per patient per year during the trial was 3.0 in the biphasic group, 5.5 in the prandial group, and 1.7 in the basal group.</p> <p>At 3 years, no differences were seen in changes from baseline in either systolic or diastolic blood pressure, high-density lipoprotein or low-density lipoprotein cholesterol, triglycerides, or the ratio of urinary albumin to creatinine, although the differences in high-density lipoprotein cholesterol were significant (P=0.03).</p>
<p>Garber et al.¹³⁰ (2007)</p> <p>Insulin detemir QD or BID and prandial insulin (insulin aspart or regular insulin) or oral antidiabetic drug treatment</p> <p>vs</p> <p>NPH insulin QD or BID and prandial insulin (insulin aspart or regular insulin) or oral antidiabetic drug treatment</p> <p>Insulin doses</p>	<p>MC, OL, PG, pooled analysis, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes for at least 1 year treated with insulin, insulin analogs, or oral antidiabetic drugs for at least 2 months, HbA_{1c} ≤12.0% (in study 3, patients with HbA_{1c} 7.5 to 10% were enrolled); patients were stratified to older (aged ≥65 years) and younger (18 to 64 years of age) subgroups</p>	<p>N=1,374</p> <p>22 to 26 weeks</p>	<p>Primary: Difference in HbA_{1c} at study endpoint between younger and older patients</p> <p>Secondary: Glucose variability, FPG, insulin doses, body weight, hypoglycemia</p>	<p>Primary: HbA_{1c} with insulin detemir was as effective as NPH after 22 to 26 weeks (mean treatment difference, 0.035%; 95% CI, -0.114 to 0.183 for older persons and 0.100%; 95% CI, -0.017 to 0.217 for younger persons; P value not reported).</p> <p>Secondary: After 22 to 26 weeks, within-person variation was significantly lower with insulin detemir than with NPH for older persons (24.3 vs 27.2 mg/dL for insulin detemir and NPH, respectively; P<0.05) and for younger persons (22.6 vs 25.8 mg/dL for insulin detemir and NPH, respectively; P<0.001).</p> <p>FPG with insulin detemir was similar to that with NPH after 24 or 26 weeks for both older and younger patients (mean treatment difference, 0.97 mg/dL; 95% CI, -8.01 to 9.95 for older persons and 4.69 mg/dL; 95% CI, -2.30 to 11.67 for younger persons; P value not reported).</p> <p>The mean daily insulin dose was 0.63±0.45 IU/kg for insulin detemir and 0.48±0.28 IU/kg for NPH in younger patients. Older patients had similar doses to younger patients (0.59±0.44 IU/kg for insulin detemir and 0.46±0.26 IU/kg for NPH; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>were adjusted to achieve target FBG 72 to 126 mg/dL, FPG <108 mg/dL, PPG <180 mg/dL or <162 mg/dL.</p>				<p>The RR for overall hypoglycemia was statistically lower with insulin detemir than with NPH in both older and younger patients (0.59; P=0.002 and 0.75; P=0.022, respectively). The RR for all nocturnal episodes was significantly lower with insulin detemir (P<0.001) in younger patients, but was not significant in older patients.</p>
<p>Raslová et al.¹³¹ (2007)</p> <p>Insulin detemir QD or BID and prandial insulin (insulin aspart or regular insulin)</p> <p>vs</p> <p>NPH insulin QD or BID and prandial insulin (insulin aspart or regular insulin)</p>	<p>PG, pooled analysis, RCT</p> <p>Patients with insulin-treated type 2 diabetes</p>	<p>N=900</p> <p>22 to 24 weeks</p>	<p>Primary: Weight gain, HbA_{1c}</p> <p>Secondary: Not reported</p>	<p>Primary: Patients taking insulin detemir had little weight gain, regardless of BMI at study entry. However, patients taking NPH had increased weight gain as baseline BMI increased (P=0.025).</p> <p>Glycemic control was similar with both treatment groups (P value not reported).</p> <p>Secondary: Not reported</p>
<p>Siegmund et al.¹³² (2007)</p> <p>Insulin glargine plus premeal rapid-acting insulin analogs</p> <p>vs</p> <p>NPH plus premeal rapid-acting insulin analogs</p>	<p>OS, PRO</p> <p>Patients with type 2 diabetes</p>	<p>N=119</p> <p>18 months</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Weight gain, incidence of hypoglycemia</p>	<p>Primary: For the insulin glargine group, results showed statistically significant reductions in HbA_{1c} compared to baseline (-0.49%; 95% CI, -0.26 to -0.71; P<0.001). However, the reduction from baseline in HbA_{1c} for the NPH group was determined to be not significant (-0.12%; 95% CI, -0.31 to 0.06; P=0.189). After 18 months, the difference between the two treatment groups was 0.37% (P<0.015).</p> <p>Secondary: Average weight gain was significantly higher in the NPH group than in the glargine group (2.10 vs 0.25 kg, respectively; P=0.025).</p> <p>Although there was a lower risk of hypoglycemia in the insulin glargine group than in the NPH group (0.50 vs 0.71 episodes/patient/month,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively), the results did not reach statistical significance (P=0.081).
Rosenstock et al. ¹³³ (2005) Insulin glargine HS vs NPH insulin QD or BID	MA MA of 4 randomized trials in type 2 diabetics comparing insulin glargine to NPH, baseline HbA _{1c} 8.8% in the insulin glargine group and 8.7% in the NPH group	N=2,304 20 to 24 weeks	Primary: Incidence of hypoglycemia Secondary: Effect on HbA _{1c} , percentage of patients reaching target HbA _{1c} (≤7.0%), effect on FPG, and insulin dose	Primary: Significant reductions in symptomatic hypoglycemic risk (-11%; P=0.0006) and nocturnal hypoglycemic risk (-26%; P<0.0001) were reported with insulin glargine compared to NPH. Secondary: No significant difference was noted between groups in HbA _{1c} reduction or percentage of patients reaching target HbA _{1c} ≤7.0%. FPG was significantly lower with insulin glargine (155 mg/dL) compared to NPH (161 mg/dL; P=0.0233). Both groups had similar mean basal and total insulin doses at all study endpoints.
Berard et al. ¹³⁴ (2015) Insulin glargine vs NPH insulin	OL, RCT Patients from the Winnipeg ACCORD trial center who were receiving basal insulin therapy with a long-acting insulin analogue	N=66 6 months	Primary: Rate of symptomatic hypoglycemia Secondary: Effect on HbA _{1c} , weight, FPG	Primary: For each hypoglycemic category, the semiannual rates ± SE per 100 patients were determined. The rates of symptomatic hypoglycemia did not differ significantly between groups, with 37.5±2.2 for the insulin glargine group and 31.1±2.1 for the NPH insulin group. Patients treated with NPH insulin had higher frequencies of severe hypoglycemia (6.1±0.9) compared with 2.7±0.6 for the insulin glargine group. The rates of nocturnal hypoglycemia were comparable between the groups, with 4.2±0.7 for the insulin glargine group and 4.4±0.8 for the NPH group. Secondary: A significant difference in HbA _{1c} changes was observed in the two groups. The mean ± SE HbA _{1c} decreases from baseline were -0.34%±0.11 for the insulin glargine group vs -0.01%±0.10 for the NPH insulin group. Changes in FPG from baseline to endpoint were not statistically significant between groups. Changes in FPG from baseline to endpoint for the insulin glargine and NPH groups were -0.98±0.34 and -0.46±0.33, respectively. Weight gain was similar in the treatment groups. Over the course of the trial, the insulin glargine-treated group experienced a 0.82±0.47 kg weight increase, while the NPH insulin-treated group showed a slight decrease of -0.08±0.44 kg.
Horvath et al. ¹³⁵	MA	N=2,293	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2007)</p> <p>Insulin analogs (insulin glargine or insulin detemir)</p> <p>vs</p> <p>NPH insulin</p>	<p>Analysis of 8 studies comparing long-acting insulin analogs to NPH in patients with type 2 diabetes</p>	<p>24 to 52 weeks</p>	<p>Change in HbA_{1c} from baseline to endpoint</p> <p>Secondary: Number of overall, severe, and nocturnal hypoglycemia</p>	<p>In a MA of studies with relevant data available comparing insulin glargine vs NPH when both agents were administered in the evening, the WMD of change of HbA_{1c} from baseline was estimated to be 0.1% (95% CI, -0.1 to 0.2; P=0.49) in favor of NPH. In all studies comparing evening insulin glargine to NPH, the WMD of change of HbA_{1c} was estimated to be 0.00% (95% CI, -0.1 to 0.1; P=0.93) which confirmed the previous result.</p> <p>In both analyses that compared change in HbA_{1c} with insulin detemir to NPH, NPH was favored (WMD, 0.1%; 95% CI, 0.01 to 0.20; P=0.03 when standard deviations were calculated and 0.2%; 95% CI, 0.02 to 0.30; P=0.08 using pooled standard deviations). Even though this result indicated a statistically significant difference in change of HbA_{1c} between insulin detemir and NPH, the difference was within the “non-inferiority” margin of 0.4% for both studies.</p> <p>Secondary: In both comparisons of insulin glargine vs NPH and insulin detemir vs NPH, both long-acting agents had statistically lower rates of severe hypoglycemia (OR, 0.70; 95% CI, 0.40 to 1.23; P value not reported and 0.50; 95% CI, 0.18 to 1.38; P=0.18, respectively).</p> <p>Insulin glargine was found to have a lower frequency of symptomatic hypoglycemia than NPH (RR, 0.84; 95% CI, 0.75 to 0.95; P=0.005). In terms of overall hypoglycemia, there was no difference in the rates of at least one hypoglycemic episode between insulin glargine in the morning, insulin glargine in the evening, and NPH at bedtime (74, 68 and 75%, respectively; P=NS).</p> <p>When comparing insulin detemir to NPH, insulin detemir had significantly lower rates of symptomatic and overall hypoglycemia (RR, 0.56; 95% CI, 0.42 to 0.74; P<0.001 and 0.82; 95% CI, 0.74 to 0.90; P<0.0001, respectively).</p> <p>Both insulin glargine and insulin detemir resulted in significantly lower rates of nocturnal hypoglycemia in comparison to NPH (RR, 0.66; 95% CI, 0.55 to 0.80; P<0.0001 and 0.63; 95% CI, 0.52 to 0.76; P<0.00001,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Bazzano et al.¹³⁶ (2008)</p> <p>Insulin glargine vs NPH insulin</p>	<p>MA, SR (12 RCTs)</p> <p>Patients with type 2 diabetes with or without oral antidiabetic agents, and not receiving insulin</p>	<p>N=4,385</p> <p>≥4 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, and body weight</p> <p>Secondary: Incidence of hypoglycemia</p>	<p>respectively).</p> <p>Primary: Changes in HbA_{1c}, FPG, and body weight demonstrate positive values favoring insulin glargine and negative values favoring NPH. The pooled net change for FPG was 0.21 mmol/L (95% CI, -0.02 to 0.45). Final HbA_{1c} was 7.9 and 7.7% with insulin glargine and insulin NPH, respectively. Pooled net change in body weight was -0.33 kg (95% CI, -0.61 to -0.06).</p> <p>Secondary: The proportions of patients reporting any (59.0 vs 53.0%; P<0.001), symptomatic (51.4 vs 42.9%; P<0.001) and nocturnal hypoglycemia (33.3 vs 19.1%; P<0.001) were significantly greater with insulin NPH. The rates of confirmed (10.0 vs 6.3%; P=0.11) and severe hypoglycemia (2.5 vs 1.4%; P=0.07) were not different between the two treatments.</p>
<p>Davidson et al.¹³⁷ (2009)</p> <p>Biphasic insulin aspart 30 (BIAsp 30) vs biphasic human insulin 30 (BHI 30)</p>	<p>MA</p> <p>Patients with type 2 diabetes who received treatment with biphasic insulin aspart 30 or biphasic human insulin 30</p>	<p>N=1,674 (9 trials)</p> <p>12 to 48 weeks</p>	<p>Primary: Overall rate of nocturnal hypoglycemia (all major, minor, and symptoms-only)</p> <p>Secondary: Major hypoglycemia, minor hypoglycemia, daytime hypoglycemia, overall hypoglycemia (the sum of all major, minor, and symptoms-only episodes), change in weight from baseline to 12 to</p>	<p>Primary: No significant difference was found between treatments with respect to the rate of overall hypoglycemia (RR, 1.08; 95% CI, 0.94 to 1.24; P=NS).</p> <p>Secondary: BIAsp 30 had a significantly lower rate of nocturnal hypoglycemia than BHI 30 (RR, 0.50; 95% CI, 0.38 to 0.67; P<0.01).</p> <p>BHI 30 was associated with a significantly lower rate of daytime hypoglycemia (RR, 1.24; 95% CI, 1.08 to 1.43; P<0.01).</p> <p>Significantly fewer patients experienced a major hypoglycemic episode with BIAsp 30 compared with BHI 30 (P<0.05).</p> <p>Rates of minor hypoglycemia were not significantly different between treatments.</p> <p>BIAsp 30 treatment was associated with a larger reduction in PPG than BHI 30 (P<0.01).</p> <p>BHI 30 treatment was associated with a significantly larger reduction in FPG than BIAsp 30 (P<0.01).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			16 weeks of treatment	<p>There were no significant differences in HbA_{1c} among the treatment groups.</p> <p>Both BIA_{sp} 30 and BHI 30 were associated with an increase in weight from base line (0.2 and 0.7 kg, respectively; P=NS).</p>
<p>Fakhoury et al.¹³⁸ (2008)</p> <p>NPH QD</p> <p>vs</p> <p>insulin detemir in the evening</p> <p>vs</p> <p>insulin glargine in the evening</p> <p>All patients remained on oral diabetes medications.</p>	<p>MA (5 OL, PG, RCTs)</p> <p>Patients between 55.5 and 61.0 years of age with type 2 diabetes who were insulin-naïve and currently receiving oral diabetes medications, with HbA_{1c} 8.6 to 9.6% and BMI of 28.5 to 32.0 kg/m²</p>	<p>N=2,092</p> <p>5 to 12 months</p>	<p>Primary: Weight gain, hypoglycemia, HbA_{1c}</p> <p>Secondary: Not reported</p>	<p>Primary: Patients receiving insulin detemir experienced significantly less weight gain compared to those receiving insulin glargine (WMD, -1.22 kg; 95% CI, -2.15 to -0.29; P=0.01).</p> <p>Fewer episodes of hypoglycemia was reported with insulin detemir compared to insulin glargine (OR, 0.52; 95% CI, 0.28 to 0.98; P=0.044).</p> <p>No significant difference was seen in the mean HbA_{1c} between insulin detemir and insulin glargine (standardized mean difference, 0.09; 95% CI, -0.16 to 0.33; P=0.48).</p> <p>No significant differences were seen in weight gain, incidence of hypoglycemia and mean HbA_{1c} between NPH and insulin glargine.</p> <p>Secondary: Not reported</p>
<p>Singh et al.¹³⁹ (2009)</p> <p>Insulin analogs</p> <p>vs</p> <p>conventional insulin</p>	<p>MA</p> <p>Adult and pediatric patients with type 1 diabetes and type 2 diabetes, and women with gestational diabetes</p>	<p>117 Trials</p> <p>4 to 30 weeks</p>	<p>Primary: HbA_{1c} and hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Adults – Type 1 Diabetes Mellitus</i></p> <p>The use of insulin lispro resulted in a lower HbA_{1c} (difference, -0.09%, 95% CI, -0.16 to -0.02), a lower risk of severe hypoglycemia (RR, 0.80; 95% CI, 0.67 to 0.96) and a lower rate of nocturnal hypoglycemia (RR, 0.51; 95% CI, 0.42 to 0.62) compared to regular insulin. For overall hypoglycemia, the rate was similar between the groups receiving insulin lispro and those receiving regular human insulin.</p> <p>For insulin aspart, the mean HbA_{1c} was lower than with regular insulin (difference, -0.13%; 95% CI, -0.20 to -0.07). There were no significant differences between treatments in the risk of severe hypoglycemia or the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>rate of overall hypoglycemia. The rate of nocturnal hypoglycemia (reported in one study) in patients receiving insulin aspart (CSII) was significantly lower than in patients receiving regular insulin (RR, 0.55; 95% CI, 0.43 to 0.70).</p> <p>There was no significant difference in HbA_{1c} (reported in one study) with insulin lispro or insulin aspart administered through CSII (difference, 0.25%; 95% CI, -0.20 to 0.71). There was also no significant difference in the rates of nocturnal hypoglycemia among the two treatment groups (RR, 1.20; 95% CI, 0.89 to 1.68). The rate of overall hypoglycemia was higher with insulin lispro than with insulin aspart (RR, 1.49; 95% CI, 1.37 to 1.63).</p> <p>Insulin glargine led to greater reductions in HbA_{1c} compared to NPH insulin (difference, -0.11%; 95% CI, -0.21 to -0.02). There were no significant differences for any type of hypoglycemia when the same bolus insulin was used in each treatment arm.</p> <p>There was no significant difference in HbA_{1c} with insulin detemir and NPH insulin (difference, -0.06%; 95% CI, -0.13 to 0.02). There was a lower risk of severe hypoglycemia (RR, 0.74; 95% CI, 0.58 to 0.96) and nocturnal hypoglycemia (RR, 0.92; 95% CI, 0.85 to 0.98) with insulin detemir compared to NPH; however, there was no difference in overall hypoglycemia.</p> <p>There was no significant difference in HbA_{1c} (reported in one study) between insulin detemir and insulin glargine (difference, -0.03%; 95% CI, -0.26 to 0.20). The risk of severe hypoglycemia (RR, 0.25; 95% CI, 0.07 to 0.86), as well as the risk for severe and nocturnal hypoglycemia were significantly lower with insulin detemir.</p> <p><i>Children and Adolescents – Type 1 Diabetes Mellitus</i> Only one trial compared insulin lispro with regular insulin in adolescents with type 1 diabetes. This study found no difference in HbA_{1c} (difference, -0.01%; 95% CI, -0.21 to 0.19) or the risk of severe hypoglycemia (RR, 1.00; 95% CI, 0.29 to 3.43) among the two treatment groups. The risk of nocturnal hypoglycemia (RR, 0.61; 95% CI, 0.57 to 0.64) and overall</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>hypoglycemia favored insulin lispro.</p> <p>There was no significant difference between insulin lispro and regular insulin in preadolescent patients for the following outcomes: HbA_{1c} (difference, 0.14%; 95% CI, -0.18 to 0.46), risk of severe hypoglycemia (RR, 0.69; 95% CI, 0.24 to 2.01), rates of nocturnal hypoglycemia (RR, 0.96; 95% CI, 0.74 to 1.26), and overall hypoglycemia.</p> <p>Only one trial compared insulin aspart and regular insulin in preadolescent patients with type 1 diabetes. This study found no difference in HbA_{1c} or risk of overall hypoglycemia among the treatment groups.</p> <p>There was no significant difference between insulin glargine and intermediate-acting insulins (mostly NPH insulin) in children and adolescents with type 1 diabetes in HbA_{1c} (difference, -0.25%; 95% CI, -0.55 to 0.05) or any type of hypoglycemia.</p> <p>Only one trial compared insulin detemir with NPH insulin in children and adolescents with type 1 diabetes. This study showed no significant differences between treatments in HbA_{1c} (difference, 0.10%; 95% CI, -0.10 to 0.30) or severe hypoglycemia (RR, 0.80; 95% CI, 0.50 to 1.28). The risk of nocturnal hypoglycemia (RR, 0.85; 95% CI, 0.77 to 0.94), as well as for nocturnal and overall hypoglycemia demonstrated small, statistically significant benefits in favor of insulin detemir.</p> <p><i>Adults – Type 2 Diabetes Mellitus</i></p> <p>There was no significant difference in HbA_{1c} (difference, -0.03%; 95% CI, -0.12 to 0.06) or risk of severe hypoglycemia (RR, 0.43; 95% CI, 0.08 to 2.37), nocturnal hypoglycemia (RR, 1.63; 95% CI, 0.71 to 3.73) or overall hypoglycemia with insulin lispro and regular insulin.</p> <p>There was no significant difference in HbA_{1c} (difference, -0.09%; 95% CI, -0.21 to 0.04) or risk of any type of hypoglycemia with insulin aspart and regular insulin.</p> <p>Only one trial compared biphasic insulin lispro and biphasic insulin aspart. This study showed no significant difference in HbA_{1c} (difference, 0.14%;</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>95% CI, -0.02 to 0.30) or overall hypoglycemia in adults with type 2 diabetes.</p> <p>Most of the studies with insulin glargine and NPH insulin have allowed the use of oral antidiabetic drugs. Only one study compared insulin glargine and NPH insulin in combination with a prandial insulin without the use of oral antidiabetic drugs. Glycemic control was no better in the insulin glargine group regardless of the type of combined therapy (difference in HbA_{1c}, -0.05%; 95% CI, -0.13 to 0.04, for insulin glargine with oral antidiabetic therapy; 0.28%, 95% CI, 0.07 to 0.49, for insulin glargine with prandial insulin). There was no significant difference in the risk of severe hypoglycemia in the studies that used oral antidiabetic therapy (RR, 0.66; 95% CI, 0.29 to 1.48). The relative risk for nocturnal hypoglycemia significantly favored insulin glargine in both the prandial insulin study (RR, 0.78; 95% CI, 0.62 to 0.98) and the studies that allowed oral antidiabetic drugs (RR, 0.56; 95% CI, 0.47 to 0.68). There was a significant reduction in risk of overall hypoglycemia in favor of insulin glargine in the studies allowing oral antidiabetic therapy but not in the bolus insulin study.</p> <p>Most of the studies with insulin detemir and NPH insulin have been conducted in patients receiving oral antidiabetic drugs. One study used prandial insulin (insulin aspart) before meals. There was a significant reduction in HbA_{1c} with NPH insulin compared to insulin detemir in studies that allowed the use of oral antidiabetic drugs (difference, 0.13%; 95% CI, 0.03 to 0.22). The risk for severe hypoglycemia was not statistically significant. The risk for nocturnal hypoglycemia (RR, 0.53; 95% CI, 0.31 to 0.91) and overall hypoglycemia significantly favored insulin detemir.</p> <p>There was no significant difference between treatment groups in terms of HbA_{1c} (difference, 0.10%; 95% CI, -0.18 to 0.38) or risk of overall hypoglycemia in the study that used prandial insulin. The risk of nocturnal hypoglycemia was lower in the insulin detemir group (RR, 0.66; 95% CI, 0.45 to 0.96).</p> <p>Two studies compared insulin detemir with insulin glargine in patients with type 2 diabetes. One of the studies allowed the use of oral antidiabetic</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>therapy and showed no significant difference in HbA_{1c} (difference, 0.10%; 95% CI, -0.06 to 0.26) or nocturnal hypoglycemia. The other study used prandial insulin (insulin aspart) and reported a higher HbA_{1c} with insulin detemir (difference, 0.20%; 95% CI, 0.10 to 0.30). There was no difference in risk of overall hypoglycemia.</p> <p><i>Pregnant Women With Diabetes</i></p> <p>There were no significant differences in HbA_{1c} with insulin lispro or regular insulin (difference, 0.20%; 95% CI, -1.03 to 1.43) or the risk of severe hypoglycemia (RR, 0.21; 95% CI, 0.01 to 4.10) among pregnant women with type 1 diabetes.</p> <p>There was no significant difference in HbA_{1c} with insulin lispro or regular insulin (difference, 0.06%; 95% CI, -0.11 to 0.23) among women with gestational diabetes.</p> <p>Results from a single trial comparing insulin aspart with regular insulin in pregnant women with type 1 diabetes were similar to those for insulin lispro in terms of HbA_{1c} (difference, -0.08%; 95% CI, -0.28 to 0.12), risk of severe hypoglycemia (RR, 1.14; 95% CI, 0.76 to 1.71) and risk of overall hypoglycemia (RR, 1.04; 95% CI, 0.98 to 1.11).</p> <p>Secondary: Not reported</p>
Intermediate-Acting and Long-acting Insulins: Type 1 and 2 Diabetes				
<p>Yenigun et al.¹⁴⁰ (2009)</p> <p>Insulin detemir QD</p> <p>Patients were originally receiving insulin glargine (QD or BID), and then were switched to insulin detemir.</p>	<p>Subgroup analysis of PREDICTIVE study (MC, OL, OS, PRO)</p> <p>Patients with type 1 or 2 diabetes, with or without concomitant oral antidiabetic agents</p>	<p>N=1,285</p> <p>12 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Changes in baseline FPG, insulin dose, and body weight; incidence of hypoglycemia; safety</p>	<p>Primary: Switching to insulin detemir significantly decreased HbA_{1c} (insulin glargine QD and type 1 diabetes, -0.47; P<0.0001, insulin glargine QD and type 2 diabetes, -0.51%; P<0.0001, insulin glargine BID and type 1 diabetes; -0.31%; P<0.05, insulin glargine BID and type 2 diabetes; -0.89%; P<0.05).</p> <p>Secondary: Significant decreases in self-monitored FPG and within-patient FPG variability were reported in patients who switched from insulin glargine QD to insulin detemir (P<0.000 for all). Results were not significant in patients who switched from insulin glargine BID because of a small</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>sample size.</p> <p>Except for type 2 diabetics who switched from insulin glargine BID, total daily insulin dose increased by 1 to 5% in patients transferring to insulin detemir.</p> <p>There was a significant decrease in body weight in patients who switched from insulin glargine QD (P<0.05). Body weight decreased in patients who switched from insulin glargine BID; however, it did not reach significance.</p> <p>On case of serious hypoglycemia was reported in a patient who switched from insulin glargine QD. No serious adverse events were reported in type 2 diabetes, although three patients experienced major hypoglycemia that were not reported as a severe adverse event. The number of hypoglycemic episodes was significantly reduced in patients with type 1 and 2 diabetes who switched from insulin glargine QD, as well as type 2 diabetes who switched from insulin glargine BID (P<0.0001). There was also a significant decrease in the number of major and nocturnal hypoglycemic events in patients who switched from insulin glargine QD (P<0.0001).</p>
Trials Comparing Insulin Devices				
<p>Ignaut et al.¹⁴¹ (2009)</p> <p>Insulin lispro administered via KwikPen[®] device</p> <p>vs</p> <p>insulin lispro administered via vial/syringe</p> <p>vs</p> <p>insulin aspart</p>	<p>OL, RCT, XO</p> <p>Patients 40 to 75 years of age with type 1 or type 2 diabetes who had been preparing and self-injecting insulin using vial and syringe for at least the previous 3 months, and who were pen device-naïve</p>	<p>N=232</p> <p>1 day</p>	<p>Primary: Preference (responses to Question 13 of the insulin device preference battery post-assessment and the final preference question)</p> <p>Secondary: Characteristics of different insulin pen devices (overall ease of</p>	<p>Primary:</p> <p>The KwikPen[®] was significantly preferred to vial and syringe, with 89% of patients preferring KwikPen[®] (95% CI, 0.8437-0.9284). KwikPen[®] was significantly preferred to FlexPen[®], with 67% of patients preferring KwikPen[®] (95% exact CI, 0.6063-0.7312). FlexPen[®] was significantly preferred to vial and syringe (81%; 95% CI, 0.7529-0.8581).</p> <p>Secondary:</p> <p>For the ease of use assessment, 94% of KwikPen[®] users and 84% of FlexPen[®] users either strongly agreed or agreed that the device was easy to use (P=0.006).</p> <p>For the ease of handling assessment, 87% of KwikPen[®] users and 73% of FlexPen[®] users either strongly agreed or agreed that the pen was easy to hold in their hand when they injected insulin (P=0.002).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
administered via FlexPen® device			use, ease of handling, ease of pressing injection button while injecting)	<p>For the ease of injection assessment, 85% of KwikPen® users and 66% of FlexPen® users either strongly agreed or agreed that the injection buttons on their respective pens were easy to press when injecting their dose (P<0.001).</p> <p>When comparing preference with the KwikPen® to vial/syringe, all comparison were statistically significant favoring KwikPen® in terms of appearance, quality of the device, discretion, convenience, use in public, easy to learn, easy to use, reliability, dose confidence, ability to follow an insulin regimen, overall satisfaction, and recommendation to others.</p>
<p>Korytkowski et al.¹⁴² (2003)</p> <p>Insulin aspart protamine and insulin aspart 70/30 mix vial/syringe for 4 weeks</p> <p>vs</p> <p>biphasic insulin aspart protamine and insulin aspart 70/30 mix prefilled pen for 4 weeks</p>	<p>OL, RCT, XO</p> <p>Patients with type 1 diabetes and type 2 diabetes were stabilized on 70% insulin aspart and 30% insulin aspart protamine then randomized to use vial/syringe or a prefilled pen for 4 weeks; after 4 weeks, patients were XO to the other administration method; baseline HbA_{1c} 8.7%</p>	<p>N=121</p> <p>12 weeks</p>	<p>Primary: Patient preference</p> <p>Secondary: Effect on glycemic control (HbA_{1c}, FPG, fructosamine, and four-point glucose profile)</p>	<p>Primary: Seventy-four percent indicated preference for prefilled pen over the vial/syringe (95% CI, 71 to 87) compared to 20% who indicated a preference for the vial/syringe.</p> <p>Secondary: Overall, a significant reduction in HbA_{1c} (-3%; P<0.05) was observed during the entire study (no comparison between treatment groups made).</p> <p>There was no significant difference in FPG, fructosamine or four-point glucose profile between treatment groups.</p> <p>There was no difference in safety profile between treatment groups.</p>
Insulin Therapy Compared to Other Antidiabetic Medications: Type 2 Diabetes				
<p>Mu et al.¹⁴³ (2012)</p> <p>Insulin glargine</p> <p>vs</p> <p>no additional</p>	<p>RCT</p> <p>Patients 35 to 50 years of age with newly diagnosed type 2 diabetes, FPG ≥9.0 mmol/L, and HbA_{1c} ≥9.0%</p>	<p>N=129</p> <p>1 year</p>	<p>Primary: Effects on β-cell function, diabetes remission rate</p> <p>Secondary: Not reported</p>	<p>Primary: Both treatment groups improved HOMA-B and HOMA-IR significantly. They had similar effects on insulin resistance (0.50±0.09 vs 0.48±0.09; P=0.23). However, the addition of insulin therapy could recover β-cell function much more than no additional treatment (2.17±0.14 vs 2.11±0.13; P=0.03).</p> <p>More patients achieved target glycemic control with the addition of insulin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>treatment</p> <p>All patients received oral antidiabetic medications.</p> <p>Active treatments were stopped after normoglycemia was maintained for 3 months.</p> <p>Patients were then followed-up with diet and physical exercise at 1 year.</p>				<p>therapy (98.3% [58 of 59]) in less time (10.4±2.5 days) compared to no additional treatment (95.7% [67 of 70] and 12.4±3.4 days). At one year follow-up, more patients maintained target glycemia without any drugs in patients who received additional insulin therapy compared to patients who received no additional treatment (37.9 vs 20.9%).</p> <p>Secondary: Not reported</p>
<p>Weissman et al.¹⁴⁴ (2014) HARMONY 4 Insulin glargine (10 U once a day) vs albiglutide (30 mg once a week)</p>	<p>MC, OL, NI, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes treated with metformin (±sulfonylurea) for at least 3 months with a baseline HbA_{1c} 7.0 to 10.0%</p>	<p>N=779</p> <p>52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to 52 weeks</p> <p>Secondary: Change from baseline in FPG at week 52, changes from baseline in HbA_{1c} and FPG over time, time to hyperglycemic rescue, proportion of patients achieving HbA_{1c} goals, body weight</p>	<p>Primary: In the albiglutide group, HbA_{1c} declined from 8.28 ± 0.90% (mean ± SD) at baseline to 7.62 ± 1.12% at week 52. A similar reduction occurred in the insulin glargine group (8.36 ± 0.95% to 7.55 ± 1.04%). The model-adjusted treatment difference of 0.11% (95% CI, -0.04 to 0.27%) indicated non-inferiority of albiglutide to insulin glargine based on the pre-specified non-inferiority margin of 0.3% (P=0.0086).</p> <p>Secondary: At week 52, FPG had declined by a mean 0.87 mmol/l in the albiglutide group and by 2.06 mmol/l in the insulin glargine group; the treatment difference was significant in favor of insulin glargine (P<0.0001). Body weight increased in the insulin glargine group and decreased in the albiglutide group, with a mean treatment difference of -2.61 kg (95% CI, -3.20 to -2.02; p<0.0001). Documented symptomatic hypoglycemia occurred in a higher proportion of patients in the insulin glargine group than in the albiglutide group (27.4 vs 17.5%, P=0.0377).</p>
<p>Giorgino et al.¹⁴⁵ (2015) AWARD-2</p>	<p>OL, MC, RCT</p> <p>Adults with an</p>	<p>N=810</p> <p>78 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to 52</p>	<p>Primary: The mean HbA_{1c} change from baseline to the 52-week primary end point was -1.08 ± 0.06%, -0.76 ± 0.06%, and -0.63 ± 0.06% for dulaglutide 1.5</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Insulin glargine once-daily vs dulaglutide 1.5 mg once-weekly vs dulaglutide 0.75 mg once-weekly</p>	<p>HbA_{1c} of ≥7.0% and ≤11.0%, BMI ≥23 and ≤45 kg/m², and stable weight for ≥3 months, who were not optimally controlled with one, two, or three oral antihyperglycemic medications (of which one had to be metformin or a sulfonylurea) for at least three months</p>		<p>weeks Secondary: Changes in HbA_{1c} from baseline to 26 and 78 weeks, the percentage of patients achieving HbA_{1c} <7.0% and ≤6.5%, and changes in FPG, 8-point self-monitored plasma glucose profiles, adverse events</p>	<p>mg, dulaglutide 0.75 mg, and glargine, respectively. Statistical criteria for superiority was met with dulaglutide 1.5 mg, LS mean difference of -0.45% (CI, -0.60 to -0.29; adjusted one-sided P<0.001). Statistical criteria for noninferiority were met for dulaglutide 0.75 mg, -0.13% (CI, -0.29 to 0.02; adjusted one-sided P<0.001). Secondary: There was no significant difference in percentages of patients who achieved the HbA_{1c} target of <7.0% for dulaglutide 0.75 mg (37.1%) compared with glargine. Greater percentages of patients on dulaglutide 1.5 mg (27.0%) and dulaglutide 0.75 mg (22.5%) achieved an HbA_{1c} target ≤6.5% than with glargine (13.5%) (P<0.001 and P=0.004, respectively). At 78 weeks, percentages of patients attaining HbA_{1c} targets were generally maintained, except for the percentage of patients with an HbA_{1c} of ≤6.5%, which was similar for dulaglutide 0.75 mg and glargine. At 52 weeks, the FPG from 8-point SMPG profiles decreased more with glargine than with dulaglutide 1.5 mg and dulaglutide 0.75 mg. More patients on dulaglutide 1.5 mg achieved HbA_{1c} targets <7.0% versus glargine (P<0.001). Body weight decreased with dulaglutide and increased with glargine. Total hypoglycemia rates were lower with dulaglutide; severe hypoglycemia was minimal. Increases in pancreatic enzymes were observed for dulaglutide. Incidence of nausea (15.4, 7.7, and 1.5%) and diarrhea (10.6, 9.2, and 5.7%) were more common with dulaglutide 1.5 mg and 0.75 mg than with glargine.</p>
<p>Okerson et al.¹⁴⁶ (2010) Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo or insulin All patients also</p>	<p>Post-hoc analysis (6 RCTs) Type 2 diabetics ≥18 years of age with HbA_{1c} ≥6.5 to ≤11.0%, BMI ≥25 to ≤45 kg/m², and stable body weight</p>	<p>N=2,171 24 to 52 weeks</p>	<p>Primary: Change in baseline BP and pulse pressure Secondary: Not reported</p>	<p>Primary: In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.20±0.56 vs 0.60±0.56 mm Hg; treatment difference, -2.80±0.75 mm Hg; P=0.002) and insulin (-4.5±0.6 vs -0.9±0.6 mm Hg; treatment difference, -3.7±0.85 mm Hg; P<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.70±0.33 vs -0.20±0.33 mm Hg; P=0.21) or insulin (-1.60±0.35 vs -0.80±0.36 mm Hg; P=0.16). No differences in the proportions of patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
received existing antidiabetic treatment regimens.				<p>-3.8 mm Hg; P=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; P<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (P values not reported).</p> <p>Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥ 40 mm Hg. In this subgroup, the reduction in pulse pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; P<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; P<0.0001).</p> <p>By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment difference, 19%; P=0.03); however, no treatment effect on DBP was observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of exenatide-treated patients were favorably shifted from a baseline classification of “abnormal DBP” to “normal DBP” compared to placebo (treatment difference, 41.4 vs 32.4%; P=0.02).</p> <p>Secondary: Not reported</p>
<p>Diamant et al.¹⁴⁷ (2010) DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients</p>	<p>OL, PG, RCT Type 2 diabetics ≥ 18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of $\geq 1,500$ mg for ≥ 8 months) or combined metformin and</p>	<p>N=456 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose</p>	<p>Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER (-1.5\pm0.05%) compared to insulin glargine (-1.3\pm0.06%; treatment difference, -0.16\pm0.07%; 95% CI, -0.29 to -0.03; P=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, HbA_{1c} was decreased by -1.5\pm0.06 and -1.4\pm0.07% (treatment difference, -1.8\pm0.08%; 95% CI, -0.34 to -0.02; P=0.031).</p> <p>Secondary: Significantly greater proportions of exenatide ER-treated patients achieved HbA_{1c} <7.0 (60 vs 48%; P=0.010) and <6.5% (35 vs 23%; P=0.004) compared to insulin glargine treated patients.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>received existing background oral glucose-lowering regimens.</p>	<p>sulfonylurea treatment ≥ 3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m², and a stable body weight ≥ 3 months</p>		<p>concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell function, insulin profile, patient-reported quality of life, safety</p>	<p>Fasting serum glucose decreased with both treatments (-2.1 ± 0.2 vs -2.8 ± 0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; $P=0.001$).</p> <p>With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points ($P<0.0001$ for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour ($P=0.022$) and before breakfast ($P<0.0001$), and significantly lower concentrations with exenatide ER were observed after dinner ($P=0.004$). Exenatide ER resulted in significantly greater reductions in post-prandial glucose excursions compared to insulin glargine after morning ($P=0.001$) and evening meals ($P=0.033$).</p> <p>Seventy nine percent of patients receiving exenatide ER experienced both a decrease in HbA_{1c} and body weight compared to 63% of patients receiving insulin glargine who experienced a decrease in HbA_{1c} and increase in body weight.</p> <p>Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; $P<0.05$). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to 0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02) observed.</p> <p>Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; $P<0.05$). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; $P<0.05$). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Both treatments resulted in improvements in IWQOL-Lite, binge eating scale, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported).</p> <p>Gastrointestinal events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. Gastrointestinal events were all mild or moderate and no serious adverse events were reported by more than one patient, except chest pain (two patients).</p>
<p>Diamant et al.¹⁴⁸ (2012) DURATION-3</p> <p>Exenatide ER 2 mg SC once weekly</p> <p>vs</p> <p>insulin glargine SC QD</p> <p>All patients received existing background oral glucose-lowering regimens.</p>	<p>ES</p> <p>Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m², and a stable body weight ≥3 months</p>	<p>N=390</p> <p>84 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportions of patients achieving HbA_{1c} <7.0 and ≤6.5%, body weight, incidence of hypoglycemia, safety</p>	<p>Primary: At 84 weeks, HbA_{1c} decreased from baseline by -1.2% with exenatide ER compared to -1.0% with insulin glargine (P=0.029).</p> <p>Secondary: The proportions of patients who achieved end point HbA_{1c} targets <7.0 and ≤6.5% were 44.6 and 36.8% with exenatide ER and insulin glargine (P=0.084) and 31.3 and 20.2% with exenatide ER and insulin glargine (P=0.009), respectively.</p> <p>Patients receiving exenatide ER lost 2.1 kg of body weight compared to patients receiving insulin glargine who gained 2.4 kg (P<0.001).</p> <p>Among patients receiving metformin plus a sulfonylurea, the incidence of minor hypoglycemia was 24 and 54% with exenatide ER and insulin glargine (P<0.001).</p> <p>Among adverse events occurring in ≥5% of all patients, diarrhea (12 vs 6%) and nausea (15 vs 1%) occurred more frequently (P<0.05) with exenatide ER compared to insulin glargine.</p>
<p>Bergenstal et al.¹⁴⁹ (2009)</p> <p>Exenatide 5 µg BID</p>	<p>OL, PG, RCT</p> <p>Patients 18 to 80 years of age with</p>	<p>N=372</p> <p>24 Weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p>	<p>Primary: At 24 weeks, HbA_{1c} values were 7.61, 7.75, 8.46% for BIAsp 30 BID, BIAsp 30 QD, and exenatide, respectively (both P<0.0001 compared to exenatide).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>for 4 weeks, then 10 µg BID</p> <p>vs</p> <p>insulin aspart 12 units QD before dinner (BIAsp 30 QD)</p> <p>vs</p> <p>insulin aspart 12 units divided equally before breakfast and dinner (BIAsp 30 BID)</p> <p>All patients were receiving metformin with or without a sulfonylurea.</p> <p>Insulin dose was titrated as necessary.</p>	<p>type 2 diabetes mellitus and HbA_{1c} ≥8.0%, insulin-naïve, and receiving treatment with metformin and a sulfonylurea for at least 3 months prior to enrolling in the study</p>		<p>Secondary: FPG, eight-point plasma glucose profiles, changes in body weight</p>	<p>At the end of the study, 37% of patients in the BIAsp 30 BID group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group (P=0.0060). Additionally, 25% of patients in the BIAsp 30 BID group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.0004).</p> <p>At the end of the study, 26% of patients in the BIAsp 30 QD group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group (P=0.3488). Additionally, 12% of patients in the BIAsp 30 QD group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.3802).</p> <p>The percentage of patients who achieved HbA_{1c} ≤6.5% was higher with BIAsp 30 BID compared to BIAsp 30 QD (25 vs 12%; P=0.0122).</p> <p>Secondary: There were significant changes in FPG with BIAsp 30 BID (-62.7 mg/dL; P<0.0001 vs exenatide) and BIAsp 30 QD (-52.4 mg/dL; P=0.0002 vs exenatide) compared to exenatide (-21.4 mg/dL).</p> <p>At the end of the study, the eight-point plasma glucose profiles were significantly lower with BIAsp 30 BID and BIAsp 30 QD than exenatide.</p> <p>At 24 weeks, hypoglycemia was reported in 56% of patients in the BIAsp 30 QD group, 61% of patients in the BIAsp 30 BID group, and 29% in the exenatide group.</p> <p>Weight loss was reported in the exenatide group (-1.9 kg) compared with weight gain in the BIAsp 30 QD (+2.8 kg) and BIAsp 30 BID (4.1 kg).</p> <p>There were more reports of nausea and vomiting with exenatide than in the insulin groups.</p>
<p>Heine et al.¹⁵⁰ (2005)</p> <p>Exenatide 5 µg BID</p>	<p>OL, RCT</p> <p>Patients 30 to 75 years of age with</p>	<p>N=551</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary:</p>	<p>Primary: At 26 weeks, similar reductions in HbA_{1c} were noted between exenatide and insulin glargine (-1.11%; CI, -0.123 to 0.157).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>for 4 weeks, then 10 µg BID</p> <p>vs</p> <p>insulin glargine QD at bedtime</p> <p>All patients were receiving existing metformin and/or sulfonylurea regimens.</p>	<p>type 2 diabetes not adequately controlled (defined as HbA_{1c} 7.0 to 10.0%) with combination metformin and sulfonylurea therapy at maximally effective doses, BMI between 25 to 45 kg/m² and a history of stable body weight (≤10% variation for ≥3 months before screening)</p>		<p>Change in FPG, fasting glucose <100 mg/dL and body weight loss</p>	<p>Secondary:</p> <p>A significantly reduction in fasting plasma glucose from baseline was observed in the insulin glargine group (−51.5 mg/dL; P<0.001). The reduction from baseline in the exenatide group was not significant (−25.7 mg/dL). A significant reduction was observed in the insulin group when compared to the exenatide group (95% CI, 20 to 34 mg/dL).</p> <p>A significantly greater proportion of patients taking insulin glargine (21.6%) achieved fasting glucose of <100 mg/dL than those taking exenatide (8.6%; P<0.001).</p> <p>A significant weight loss was experienced in the exenatide group (−2.3 kg) compared to a gain of +1.8 kg in the insulin group (CI, −4.6 to −3.5; P<0.001).</p> <p>Similar rates of hypoglycemia were reported with both agents (CI, −1.3 to 3.4 events/patient-year). Exenatide patients had a higher incidence of daytime hypoglycemia (CI, 0.4 to 4.9 events/patient-year), and a lower rate of nocturnal hypoglycemia than insulin glargine patients (CI, −2.3 to −0.9 events/patient-year).</p> <p>A significantly higher incidence of gastrointestinal side effects, including nausea (57.1 vs 8.6%; P<0.001), vomiting (17.4 vs 3.7%; P<0.001) and diarrhea (8.5 vs 3%; P=0.006), upper abdominal pain (P=0.012), constipation (P=0.011), dyspepsia (P=0.011), decreased appetite (P=0.021), and anorexia (P=0.002) were reported in the exenatide group vs the insulin group.</p> <p>Withdrawals due to adverse events occurred in 9.5% of exenatide patients vs 0.7% of insulin patients.</p>
<p>Secnik Boye et al.¹⁵¹ (2006)</p> <p>Exenatide 5 µg BID for 4 weeks, then 10 µg BID</p>	<p>MC, OL, RCT</p> <p>Secondary analysis on patients with type 2 diabetes inadequately controlled (defined</p>	<p>N=455</p> <p>26 weeks</p>	<p>Primary:</p> <p>Patient-reported health outcome measures: Diabetes Symptom Checklist-revised, DTSQ, EQ-5D,</p>	<p>Primary:</p> <p>Both exenatide and insulin glargine groups experienced a significant improvement from baseline in patient-reported health outcome measures as demonstrated by Diabetes Symptom Checklist-revised overall scores, DTSQ, EQ-5D and Medical Outcomes Study 36-Item Short-Form Health Survey scores (P<0.05 for all measures). There was not a statistical difference between treatment groups in any of the outcome measures</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>insulin glargine QD at bedtime</p> <p>All patients were receiving existing metformin and/or sulfonylurea regimens.</p>	<p>as an HbA_{1c} between 7.0 and 10.0%) with sulfonylurea and metformin therapy at maximally effective doses, enrolled in a previous 26 week study</p>		<p>Medical Outcomes Study 36-Item Short-Form Health Survey, Diabetes Medical Outcomes Study 36-Item Short-Form Health Survey</p> <p>Secondary: Not reported</p>	<p>(P>0.05 for all measures).</p> <p>Neither the exenatide nor the insulin glargine group experienced a significant improvement in Medical Outcomes Study 36-Item Short-Form Health Survey scores (P=0.93 for both groups).</p> <p>Secondary: Not reported</p>
<p>Nauck et al.¹⁵² (2007)</p> <p>Exenatide 5 µg BID for 4 weeks, then 10 µg BID</p> <p>vs</p> <p>insulin aspart BID</p> <p>All patients were receiving existing metformin and/or sulfonylurea regimens.</p>	<p>MC, OL, RCT</p> <p>Patients 30 and 75 years of age who had suboptimal glycemic control despite receiving optimally effective metformin and sulfonylurea therapy for ≥3 months, HbA_{1c} ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m², and a history of stable body weight (≤10% variation for ≥3 months)</p>	<p>N=501</p> <p>52 weeks</p>	<p>Primary: Mean change in HbA_{1c} levels, weight, fasting serum glucose levels, postprandial glucose levels, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: There was not a significantly different change from baseline in mean HbA_{1c} levels between the exenatide (−1.04%) and insulin aspart groups (−0.89%, 95% CI, −0.32% to 0.01%; P=0.067).</p> <p>Patients in the exenatide group experienced a gradual weight loss of −2.5 kg, compared to a gradual weight gain of 2.9 kg in the insulin aspart group, (95% CI, −5.9 to −5.0; P<0.001) at the end of 52 weeks.</p> <p>Patients in both exenatide (−1.8 mmol/L) and insulin aspart (−1.7 mmol/L) groups had a significant decrease in fasting serum glucose compared to baseline (P<0.001 for both groups). There was not a significant difference between groups (CI, −0.6 to 0.4; P=0.689).</p> <p>Patients in the insulin aspart group had significantly lower mean glucose values at pre-breakfast (P=0.037), pre-lunch (P=0.004) and 03.00 hours (P=0.002). Patients in the exenatide group had a greater reduction in postprandial glucose excursions following morning (P<0.001), midday (P=0.002) and evening meals (P<0.001).</p> <p>The withdrawal rate was 21.3% in the exenatide group and 10.1% in the insulin aspart group. Adverse events that were more commonly reported in the exenatide vs insulin aspart group included: nausea (33.2 vs 0.4%), vomiting (15.0 vs 3.2%), diarrhea (9.5 vs 2%) and other clinically relevant adverse events (13.4 vs 6.4%).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Xu et al.¹⁵³ (2015) CONFIDENCE</p> <p>Exenatide twice daily vs insulin (75% insulin lispro protamine suspension and 25% insulin lispro injection) twice daily vs pioglitazone once daily</p>	<p>MC, PG, RCT</p> <p>Treatment-naïve patients 30 to 70 years of age with newly diagnosed type 2 diabetes</p>	<p>N=416</p> <p>48 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Effects on weight, blood pressure, lipid profiles and β-cell function</p>	<p>Secondary: Not reported</p> <p>Primary: At week 48, mean (95% CI) HbA_{1c} changes from baseline were -1.8% (-1.55 to -2.05%) with exenatide, -1.7% (-1.52 to -1.96%) with insulin and -1.5% (-1.23 to -1.71%) with pioglitazone. Treatment differences were -0.20% (95% CI, -0.46 to 0.06%) for exenatide vs insulin (P=0.185), and -0.37% (95% CI, -0.63 to -0.12%) for exenatide vs pioglitazone (P=0.002).</p> <p>Secondary: Mean weight change was significantly different between the exenatide group and the insulin and pioglitazone groups from weeks four and eight until the end of the study, with weight decreasing in the exenatide group. Decreases in mean systolic and diastolic blood pressures at 48 weeks were not statistically different between groups, although significant decreases in systolic and diastolic blood pressures were observed with exenatide (P<0.05 vs baseline), and a significant decrease in diastolic blood pressure alone was found with pioglitazone (P<0.001). Exenatide treatment resulted in improvements in overall lipid profiles, with significant decreases in TG, total cholesterol and LDL cholesterol levels, and an increase in HDL cholesterol (P<0.05 vs baseline for all variables). HDL cholesterol increased with pioglitazone (P<0.001), and LDL cholesterol decreased with insulin (P<0.05).</p> <p>At week 48, HOMA-B (which, together with fasting proinsulin-to-insulin ratio (PI/I), provides an indication of β-cell function during the fasting state) increased in patients treated with insulin (P<0.001 vs baseline). Improvements from baseline were similar in all treatment groups with regard to PI/I, as well as acute insulin response (AIR, which represents β-cell function during the stimulated state after intravenous glucose injection). Disposition index (DI), which provides a measure of β-cell function during the stimulated state under near-physiological conditions of food intake via the gastrointestinal system, increased significantly in all treatment groups (P<0.001 vs baseline for exenatide; P<0.05 vs baseline for insulin and pioglitazone). The greatest mean improvements from baseline in DI and AIR were observed in the exenatide treatment group.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Hollander et al.¹⁵⁴ (2015)</p> <p>Insulin glargine+ one oral antidiabetes drug (metformin or sulfonylurea) wherein previous TZD therapy was dropped and replaced with insulin glargine (GLAR +1 OAD)</p> <p>vs</p> <p>three oral antidiabetes drugs (3OAD) wherein patients receiving TZD and metformin received add-on sulfonylurea (glyburide) and patients receiving TZD and sulfonylurea received add-on metformin (3OAD)</p>	<p>MC, OL, RCT</p> <p>Type 2 diabetes patients 18 to 79 years of age with a HbA_{1c} of 7.5 to 12.0% despite ≥3 months of treatment with a TZD plus metformin or a sulfonylurea</p>	<p>N=337</p> <p>48 weeks</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: Changes in FPG, weight, BMI, and serum lipid profile</p>	<p>Primary: Substitution of insulin glargine for a TZD and addition of a third OAD resulted in an adjusted mean change in HbA_{1c} from baseline of -1.66% and -1.86%, respectively (adjusted mean difference 0.20; 95% CI, -0.11 to 0.51). The upper limit of the 95% CI for the difference in the adjusted mean changes from baseline to endpoint for HbA_{1c} was 0.51%; therefore, the primary efficacy analysis did not demonstrate equivalent glycemic control during treatment with GLAR + 1 OAD and 3OAD as measured by HbA_{1c} levels. In patients originally taking sulfonylurea, there was a significantly greater reduction in HbA_{1c} in those adding metformin to TZD and sulfonylurea versus those switching the TZD for GLAR + SU at weeks 12, 24, and 48.</p> <p>Secondary: Adjusted mean FPG at baseline was similar between the two treatment arms (GLAR + 1 OAD 193.0 mg/dL vs 3OAD 199.5 mg/dL; P=0.4299). FPG reduced significantly from baseline to endpoint (P<0.0001 for both arms).</p> <p>Weight gain was observed in both treatment arms at each study visit and at endpoint. At each visit, patients in the GLAR + 1 OAD arm gained less weight than those in the 3OAD arm; this difference was significant at week 12 (P=0.0035). A similar pattern was observed for BMI.</p> <p>Overall, insulin glargine + metformin was as effective as 3OAD in achieving glycemic control but with greater improvements in lipid parameters, less weight gain, and lower hypoglycemia rates.</p>
<p>Kabadi et al.¹⁵⁵ (2003)</p> <p>Tolazamide 1 gram daily plus premixed 70% NPH and 30%</p>	<p>PC, RCT</p> <p>Patients with type 2 diabetes mellitus with a lapse of glycemic control,</p>	<p>N=40</p> <p>7 months</p>	<p>Primary: Changes in body weight, HbA_{1c}, and fasting C-peptide concentrations</p>	<p>Primary: Changes in body weight were 2.5±0.8 kg for the tolazamide group, 2.6±1.0 kg for the glyburide group, 2.4±0.9 kg for the glipizide XL group, and 2.2±0.7 kg for the glimepiride group, all were significant compared to placebo (P<0.01) after the addition of insulin.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>regular insulin daily vs glyburide 20 mg daily plus premixed 70% NPH and 30% regular insulin daily vs glipizide XL plus premixed 70% NPH and 30% regular insulin daily vs glimepiride 8 mg daily plus premixed 70% NPH and 30% regular insulin daily vs placebo plus premixed 70% NPH and 30% regular insulin daily</p>	<p>established by documentation of HbA_{1c} >7.4% on ≥2 occasions at an interval of ≥3 months in each patient while taking oral sulfonylureas consisting of one of these drugs in the maximum recommended daily dose: tolazamide 1 g daily, glyburide 20 mg daily, glipizide XL 20 mg daily, or glimepiride 8 mg daily</p>		<p>Secondary: Changes in daily insulin dose and the number of hypoglycemic episodes confirmed by finger stick blood glucose <60 mg/ dL</p>	<p>All groups achieved optimal glycemic control as expressed by HbA_{1c} <7.4%, 1% above the highest normal level of 6.4% in our laboratory as recommended by the American Diabetes Association after the addition of insulin. HbA_{1c} was 6.8±0.4% for tolazamide, 6.9±0.4% for glyburide, 6.7±0.4% for glipizide XL, 6.7±0.3% for glimepiride, and 7.0±0.3% for placebo.</p> <p>C-peptide levels decreased in all groups. The reduction in the C-peptide level was significantly greater (P<0.05) in the placebo group compared to the sulfonylurea groups. There were no significant differences among the sulfonylurea groups.</p> <p>Secondary: Patients receiving sulfonylureas required a significantly lower (P<0.01) daily insulin dose, as well as dose per kilogram of body weight in comparison to patients receiving placebo (P<0.01).</p> <p>The daily insulin dose and units per kilogram of body weight was significantly lower (P<0.05) in patients receiving glimepiride in comparison to those receiving tolazamide, glyburide, or glipizide XL.</p> <p>The number of hypoglycemic episodes during the last four weeks of the study were significantly lower in the sulfonylurea groups as compared to the placebo group (P<0.01). The differences among the individual sulfonylurea groups were not significantly different.</p>
<p>Russell-Jones et al.¹⁵⁶ (2009) LEAD-5 Liraglutide 1.8 mg SC QD</p>	<p>PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with oral glucose lowering agents ≥3 months before</p>	<p>N=581 26 weeks</p>	<p>Primary: Change in baseline in HbA_{1c} Secondary: Change in baseline body weight, waist</p>	<p>Primary: Decreases in HbA_{1c} were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -1.09%; 95% CI, -1.28 to -0.90; P<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; P=0.0015).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs placebo vs insulin glargine (OL)</p> <p>All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day.</p>	<p>screening, HbA_{1c} 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination therapy), and BMI ≤45 kg/m²</p>		<p>circumference, FPG, eight-point self-monitored glucose concentrations, β cell function, and BP</p>	<p>The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; P=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; P<0.0001).</p> <p>The decrease in waist circumference with liraglutide (-1.50 cm) was significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; P<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; P=0.0608).</p> <p>Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; P<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported).</p> <p>Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin (-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; P<0.0001), but not compared to insulin (data not reported).</p> <p>Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, -0.00366; 95% CI, -0.00597 to -0.00136; P=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; P<0.0001) were achieved with liraglutide.</p> <p>A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; P=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; P=0.0791). No significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin.</p>
Civera et al. ¹⁵⁷	OL, PG	N=37	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2008)</p> <p>Repaglinide 2 mg TID before meals plus metformin 850mg BID plus NPH insulin before dinner</p> <p>vs</p> <p>metformin 850mg BID plus NPH insulin before dinner</p> <p>vs</p> <p>NPH insulin BID</p>	<p>Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs</p>	<p>24 weeks</p>	<p>HbA_{1c}, hypoglycemia, body weight</p> <p>Secondary: Not reported</p>	<p>The HbA_{1c} was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; P=0.02) and the NPH insulin group (8.4%; P=0.02).</p> <p>The absolute reduction in HbA_{1c} was -2.4% in the repaglinide triple therapy group compared to -0.7% (P=0.01) in the metformin plus NPH insulin group and -1.4% in the insulin NPH group.</p> <p>Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (P<0.01).</p> <p>Significant differences in weight gain and hypoglycemia were not seen.</p> <p>Secondary: Not reported</p>
<p>Cesur et al.¹⁵⁸ (2007)</p> <p>Repaglinide up to 4 mg QD</p> <p>vs</p> <p>glimepiride up to 8 mg QD</p> <p>vs</p> <p>insulin glargine up to 36 U QD</p>	<p>MC, OL, OS, PRO</p> <p>Patient 33 to 67 years of age with type 2 diabetes, HbA_{1c} 6.0 to 8.0% taking oral diabetes agents, who were willing to fast throughout Ramadan month</p>	<p>N=65</p> <p>Duration not specified</p>	<p>Primary: FBG, PPG, HbA_{1c}, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and post-Ramandan fasting</p> <p>Secondary: Not reported</p>	<p>Primary: In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan.</p> <p>In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan (P<0.05 and P<0.01, respectively). At post-Ramadan and one-month post-Ramadan, changes in PPG values in the fasting group were lower compared to the nonfasting group (P<0.01 for both time periods).</p> <p>There was no significant change in HbA_{1c} levels between the nonfasting and fasting groups.</p> <p>There was a significant increase in fructosamine levels in both fasting group and non-fasting group at one-month post-Ramadan (P<0.01 for both).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group (P<0.05 between pre-Ramadan and post-Ramadan in nonfasting group).</p> <p>TC, LDL-C and TG did not change throughout the study period but HDL-C levels significantly increased at post-Ramadan in the fasting group (P<0.01). In nonfasting group, LDL-C and TG levels significantly increased at post-Ramadan (P<0.05 for both).</p> <p>At least one hypoglycemia episode was reported in 12.2% of patients in the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia.</p> <p>Secondary: Not reported</p>
<p>Chisalita et al.¹⁵⁹ (2009)</p> <p>Repaglinide 4mg TID before meals for 10 weeks</p> <p>vs</p> <p>insulin aspart 13 to 46 units/day (4 to 20 units at breakfast, 5 to 15 units at lunch and 4 to 15 units at dinner) for 10 weeks</p>	<p>XO</p> <p>Patients ≥60 years of age with type 2 diabetes</p>	<p>N=5</p> <p>20 weeks</p>	<p>Primary: HbA_{1c}, blood glucose, C-peptide, free human insulin, free total (human and analogue) insulin, proinsulin, islet amyloid polypeptide, growth hormone binding protein, and plasma lipoprotein concentrations were measured</p> <p>Secondary: Not reported</p>	<p>Primary: The HbA_{1c} was 6.1% at the end of repaglinide therapy and 5.9% at the end of insulin aspart therapy (P=NS).</p> <p>C-peptide concentrations were significantly higher during repaglinide treatment compared to insulin aspart treatment (AUC 2,453 vs 1,153; P=0.02).</p> <p>Free human insulin levels were significantly higher on repaglinide than on insulin aspart therapy (AUC 215 vs 128; P<0.05).</p> <p>Proinsulin levels were higher when measured during repaglinide treatment than during treatment with insulin aspart.</p> <p>Islet amyloid polypeptide levels tended to be higher during repaglinide compared to insulin aspart treatment (P=NS).</p> <p>Fasting plasma insulin like growth factor-I concentration was 220 ng/mL during treatment with insulin aspart and 226 ng/mL during treatment with repaglinide (P=NS).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Compared to fasting levels, the insulin like growth factor binding protein-1 levels were lower during repaglinide (P<0.05), but not during insulin aspart treatment (P=NS).</p> <p>Repaglinide treatment increased plasma growth hormone binding protein concentration compared with insulin aspart (1,094 vs 942 pmol/L; P=0.02).</p> <p>Repaglinide treatment resulted in higher postprandial plasma TC, TG and apolipoprotein B concentrations compared with insulin aspart. There was no significant difference in LDL-C or HDL-C</p> <p>Secondary: Not reported</p>
<p>Meneghini et al.¹⁶⁰ (abstract) (2010)</p> <p>Insulin glargine vs pioglitazone</p>	<p>MC, OL, PG</p> <p>Adults with poorly controlled type 2 diabetes (HbA_{1c} 8.0 to 12.0%), despite ≥3 months of sulfonylurea or metformin monotherapy</p>	<p>N=389</p> <p>48 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, BMI, body weight, safety</p>	<p>Primary: At trial end, insulin glargine resulted in a significantly greater reduction in HbA_{1c} compared to pioglitazone (-2.48 vs -1.86%; 95% CI, -0.93 to -0.31; P=0.001).</p> <p>Secondary: Insulin glargine resulted in significantly greater reductions in FPG at all time points (trial end difference, -34.9 mg/dL; 95% CI, -47.6 to -22.2; P<0.0001).</p> <p>Changes in weight and BMI were similar between the two treatments.</p> <p>Compared to pioglitazone, insulin glargine resulted in a lower overall incidence of possibly treatment-emergent adverse events (12.0 vs 20.7%) and fewer study discontinuations (2.2 vs 9.1%), but a higher rate (per patient-year) of confirmed clinically relevant hypoglycemic episodes (4.97 vs 1.04; P<0.0001) and severe hypoglycemia (0.07 vs 0.01; P=0.0309).</p>
<p>Dorkhan et al.¹⁶¹ (2008)</p> <p>Pioglitazone 30 to 45 mg QD and existing oral</p>	<p>RCT, OL</p> <p>Patients with type 2 diabetes and inadequate glycemic control (defined as</p>	<p>N=36</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c}, β-cell function, insulin sensitivity, degree of patient satisfaction</p>	<p>Primary: After 26 weeks, the change in HbA_{1c} from baseline was -1.3% (P<0.01) for pioglitazone and -2.2% (P<0.01) for insulin glargine. There was no significant difference between the treatment groups (P=0.050).</p> <p>There was no difference in insulin, β-cell function, or insulin sensitivity</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>hypoglycemic therapy</p> <p>vs</p> <p>insulin glargine 6 to 10 IU/day administered in the morning (titrated as necessary) and existing oral hypoglycemic therapy</p>	<p>treatment with metformin and sulfonylurea/ meglitinide in doses $\geq 50\%$ of maximum recommended doses and HbA_{1c} >6.2%</p>		<p>Secondary: Not reported</p>	<p>among the two treatment groups (P value not significant). Insulin glargine resulted in a greater reduction in proinsulin concentrations than pioglitazone (-55 vs -25%; P<0.01).</p> <p>Pioglitazone increased HDL-C (0.14 mmol/L) compared to a slight decrease in the insulin glargine group (-0.04 mmol/L; P<0.01 between groups). There were no significant differences between the treatment groups with regards to other lipid parameters (P value not significant).</p> <p>The degree of satisfaction with treatment was similar in the pioglitazone and insulin glargine treatment groups.</p> <p>There was a doubling of serum adiponectin levels in the pioglitazone group (7.5 to 15; P<0.01) compared to a significant decrease in the insulin glargine group (8.7 to 7.6; P=0.04; P<0.01 between groups).</p> <p>Secondary: Not reported</p>
<p>Aljabri et al.¹⁶² (2004)</p> <p>Pioglitazone 30 to 45 mg QD</p> <p>vs</p> <p>NPH insulin 0.3 unit/kg QD</p> <p>All patients were receiving existing sulfonylurea or metformin therapy</p>	<p>OL, RCT</p> <p>Patients with poorly controlled type 2 diabetes (HbA_{1c} >8%) with insulin secretagogues and metformin monotherapy</p>	<p>N=62</p> <p>16 weeks</p>	<p>Primary: Effect on HbA_{1c}, FPG, incidence of hypoglycemia (< 68 mg/dL), effect on lipoproteins, quality of life (assessed using the DTSQ)</p> <p>Secondary: Not reported</p>	<p>Primary: Similar reductions in HbA_{1c} were observed in pioglitazone-treated (-1.9%) and NPH insulin-treated patients (-2.3%; P=0.32).</p> <p>Nonsignificant differences in reduction in FPG were observed with NPH insulin (-77 mg/dL) and pioglitazone (-52 mg/dL; P=0.07).</p> <p>Significantly more patients reported hypoglycemia with NPH insulin (19) than with pioglitazone (11; P=0.02).</p> <p>Significant increases in HDL-C were observed with pioglitazone (4 mg/dL) compared to NPH insulin (0 mg/dL; P=0.02).</p> <p>No significant differences in total cholesterol, LDL cholesterol and triglycerides were reported between the two treatment groups.</p> <p>No significant differences were noted for the DTSQ scores between the two treatment groups.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Ligvay et al.¹⁶³ (2009)</p> <p>Pioglitazone 15 to 45 mg QD plus glyburide 1.25 mg BID</p> <p>vs</p> <p>insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily</p> <p>All patients were receiving metformin 1,000 mg BID</p> <p>Doses of medications could be titrated at the investigator's discretion.</p>	<p>RCT, OL</p> <p>Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve</p>	<p>N=58</p> <p>36 months</p>	<p>Primary: HbA_{1c}, rate of treatment failures (defined as HbA_{1c} >8.0%), hypoglycemia, weight gain, compliance, QOL, and patient satisfaction</p> <p>Secondary: Not reported</p>	<p>Secondary: Not reported</p> <p>Primary: After 36 months, HbA_{1c} was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26).</p> <p>The percentage of patients achieving HbA_{1c} <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the HbA_{1c} goal at the end of 36 months.</p> <p>Three patients in each group reached the “treatment failure” end point.</p> <p>The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53).</p> <p>In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) versus 3.36 kg (-0.47 to 7.20; P=0.04).</p> <p>Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group.</p> <p>There were differences between the groups for any of the 12 QoL domains evaluated.</p> <p>All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization.</p> <p>Secondary: Not reported</p>
<p>Ibrahim et al.¹⁶⁴ (2013)</p> <p>Group I: oral metformin (500 mg</p>	<p>NI, RCT</p> <p>Pregnant women with gestational or pre-existing</p>	<p>N=90</p> <p>Variable duration</p>	<p>Primary: Maternal glycemic control</p> <p>Secondary:</p>	<p>Primary: Glycemic control was achieved in 76.1% of patients in group I and 100% of patients in group II (P=0.001).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
T1D) without increasing the insulin dose vs group II: increased insulin dose	DM at gestations between 20 and 34 weeks who showed insulin resistance (defined as poor glycemic control at a daily dose of ≥ 1.12 units/kg)		Maternal hypoglycemia, hospital admissions, neonatal outcomes	Readmission for poor glycemic control was not significantly different between groups (P=0.471). Bouts of maternal hypoglycemia occurred in 6.5% of patients in group I and 22.7% in group II (P=0.029). Only two neonatal/delivery outcomes showed a statistical difference: Neonatal hypoglycemia occurred in 7.0% of cases in group I vs 38.5% in group II (P=0.001). Neonatal Intensive Care Unit admission occurred in 18.6% of group I neonates and 41% of group II neonates (P=0.026).
Spaulonci et al. ¹⁶⁵ (2013) Metformin vs insulin	PRO, RCT Women with gestational diabetes with singleton pregnancy, use of diet and exercise for a minimum period of 1 week without satisfactory glycemic control, absence of risk factors for lactic acidosis, and absence of anatomic and/or chromosome anomalies of the conceptus detected by ultrasonography.	N=92 Variable duration	Primary: Maternal glycemic control Secondary: Neonatal outcomes	Primary: Higher mean glucose levels were observed in the insulin group (P=0.020), mainly because of higher levels observed after dinner (P=0.042). Twenty-one percent of women using insulin and 27% of women using metformin achieved adequate glycemic control in the first week of treatment (P=0.11). Twelve (26.08%) of the 46 women in the metformin group required supplemental insulin for adequate glycemic control. Secondary: No significant differences between the two groups were observed regarding the following neonatal outcomes: gestational age at birth, 1-minute Apgar score, 5-minute Apgar score, umbilical artery pH at birth, or newborn weight. There were no fetuses with macrosomia in the group metformin vs three (6.5%) cases in the insulin group (P=0.242). A higher frequency of neonatal hypoglycemia was observed in cases treated with insulin (22.2%) compared with newborns from the metformin group (6.5%) (P=0.032).
Niromanesh et al. ¹⁶⁶ (2012) Metformin vs insulin	RCT, SB Gestational diabetes mellitus women with singleton pregnancy and gestational age between 20 and 34 weeks who did not achieve glycemic	N=160 Variable duration	Primary: Maternal glycemic control, birth weight Secondary: Neonatal and obstetric complications	Primary: The two groups were comparable with respect to mean fasting blood sugar and postprandial measurements throughout pregnancy after randomization until delivery. The mean fasting blood sugar was <95 mg/dL in 74% and 79% of women in the metformin and insulin groups, respectively (P=0.457). Neonates from the metformin group had a significantly lower circumference of head, arm and chest (P<0.05) and had lower birth weight (P=0.005) and height (P=0.033). The frequency rate of SGA (small for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	control on diet			<p>gestational age; birth weight < 10th percentile) was 3.8% in the metformin group and 2.5% in the insulin group. The relative risk of LGA (large for gestational age; birth weight > 90th percentile) in the metformin group was half that of the insulin group (RR, 0.5; 95% CI, 0.3 to 0.9, P=0.012).</p> <p>Secondary: The relative risk of emergency cesarean and preterm delivery was 1.6 and 2.2 times higher, respectively, in the metformin group; however, this was not statistically significant. The two groups were not statistically different in terms of need for phototherapy, incidence of hypoglycemia, and birth defects. The two groups were comparable with respect to umbilical artery pH, Apgar score at 5 min, and hospitalization days. Neonatal Intensive Care Unit admission and respiratory distress syndrome was nonsignificantly more frequent in the metformin group (RR, 2.5; 95% CI, 0.5 to 12.5, P=0.443).</p>
<p>Poolsup et al.¹⁶⁷ (2014)</p> <p>Pool A: metformin vs insulin</p> <p>Pool B: glyburide vs insulin</p>	<p>MA</p> <p>Women with gestational diabetes mellitus</p>	<p>N=2,151 (13 RCTs)</p> <p>Variable duration</p>	<p>Primary: Safety and efficacy of oral antidiabetic agents compared to insulin</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p><u>Pool A</u></p> <p>There was a nonsignificant difference in the risk of macrosomia (RR, 0.93; 95% CI, 0.61 to 1.41) and large for gestational age (LGA) births (RR, 0.88; 95% CI, 0.70 to 1.12) between the two study groups. A significant increase in the risk of preterm births occurred in the metformin group as compared to insulin (RR, 1.51; 95% CI, 1.04 to 2.19; P=0.03). Rate of neonatal/perinatal mortality was very low in both groups and results remained statistically non-significant. Risk of shoulder dystocia, neonatal hypoglycemia, congenital abnormality, and small for gestational age (SGA) births tended to be lower with metformin but statistical significance was not achieved. A non-significant decrease in risk of caesarean section, pre-eclampsia, and labor induction was noticed with metformin compared to insulin. A significant decrease in the risk of gestational hypertension was observed in the metformin arm (RR, 0.54; 95% CI, 0.31 to 0.91; P=0.02). A significant decrease in PPG levels occurred (mean difference, -2.47 mg/dL; 95% CI, -4.00 to -0.94, P=0.002) in metformin group compared to insulin, while results were statistically nonsignificant between the two groups for FPG levels (mean difference, 0.74 mg/dL; 95% CI, -0.52 to -2.01).</p> <p><u>Pool B</u></p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Glyburide significantly increased the risk of macrosomia (RR, 3.07; 95% CI, 1.14 to 8.23; P=0.03) and neonatal hypoglycemia (RR, 2.30; 95% CI, 1.28 to 4.11; P=0.005) compared to insulin. There was no difference between glyburide and insulin with regard to risk for LGA births; statistically significant heterogeneity was detected for this outcome. There were no significant differences in the risk of preterm births, neonatal mortality, congenital abnormality, or SGA births for glyburide versus insulin. None of the maternal outcomes (caesarean section, pre-eclampsia, maternal hypoglycemia, glycemic levels) displayed a significant difference between glyburide and insulin. The effect estimate for fasting glucose levels (mean difference, 1.90 mg/dL; 95% CI, -0.38 to 4.18) and postprandial glucose levels (mean difference, 3.42 mg/dL; 95% CI, -1.17 to 8.02) favored the insulin group, but results remained nonsignificant.</p> <p>Secondary: Not reported</p>
<p>Nichols et al.¹⁶⁸ (2007)</p> <p>Metformin vs sulfonylurea vs insulin vs TZDs</p>	<p>MC, OS, RETRO</p> <p>Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies</p>	<p>N=9,546</p> <p>≥12 months</p>	<p>Primary: Weight changes</p> <p>Secondary: Not reported</p>	<p>Primary: Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant.</p> <p>Secondary: Not reported</p>
<p>Black et al.¹⁶⁹ (2007)</p> <p>Meglitinide</p>	<p>MA (15 trials)</p> <p>Patients with type 2 diabetes</p>	<p>N=3,781</p> <p>Duration varied</p>	<p>Primary: Mortality and morbidity</p> <p>Secondary:</p>	<p>Primary: No trials reported the effect of meglitinides on mortality and morbidity.</p> <p>Secondary: In the 11 trials comparing meglitinides to placebo, both repaglinide and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs meglitinide plus metformin vs meglitinide plus insulin vs metformin vs placebo			Change in HbA _{1c} , weight or BMI, hypoglycemia, adverse effects, quality of life	<p>nateglinide resulted in reductions in HbA_{1c} (0.1 to 2.1% and 0.2 to 0.6%, respectively). In two trials comparing repaglinide to nateglinide, reduction in HbA_{1c} was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in HbA_{1c} compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in HbA_{1c} compared to metformin.</p> <p>Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin.</p> <p>Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides.</p> <p>There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes.</p> <p>There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization DTSQ improved significantly in patients receiving repaglinide compared to patients receiving placebo.</p>
Saenz et al. ¹⁷⁰ (2005) Metformin monotherapy vs	MA (29 RCTs) Adult patients with type 2 diabetes	N=5,259 ≥3 months	Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia,	Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide†, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03). Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo, sulfonylureas, TZDs, meglitinides, α -glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin			fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photo-coagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypoglycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA _{1c} , FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow	related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02). Secondary: Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA _{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.
Monami et al. ¹⁷¹ (2011)	MA (53 trials)	N=33,881	Primary: Incidence of cancer	Primary: There were 176 cases of cancer (107 and 69 in patients receiving DPP-4

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>DPP-4 inhibitors (linagliptin, alogliptin, sitagliptin, saxagliptin, vildagliptin*)</p> <p>vs</p> <p>placebo or active comparator (oral hypoglycemic agents and/or insulin)</p>	<p>Patients with type 2 diabetes who were receiving a DPP-4 inhibitor</p>	<p>≥24 weeks</p>	<p>Secondary: Incidence of pancreatitis, all-cause and cardiovascular mortality, incidence of major cardiovascular events</p>	<p>inhibitors and comparators, respectively); 12.5% were gastrointestinal, 5.7% were pancreatic, 6.2% were pulmonary, 14.7% were mammary gland/female genital tract, 11.3% were male urogenital tract, 3.4% were thyroid, and 26.1% were of another origin. There was no difference in the proportion of cases between patients receiving DPP-4 inhibitors or a comparator (P=0.90).</p> <p>Secondary: The risk of pancreatitis with DPP-4 inhibitors was 0.786 (P=0.55).</p> <p>The number of reported deaths was 28 and 31 with DPP-4 inhibitors and comparators, respectively. Cardiovascular deaths occurred in 10 patients receiving DPP-4 inhibitors and 20 patients receiving comparators. The risk for all-cause death and cardiovascular death in patients receiving DPP-4 inhibitors was 0.668 (P=0.149 and P=0.054, respectively).</p> <p>There were 137 and 120 major cardiovascular events reported with DPP-4 inhibitors and comparators, respectively. DPP-4 inhibitors were associated with a significantly lower risk of major cardiovascular events (OR, 0.689; P=0.006).</p>
<p>Shyngdan et al.¹⁷² (2011)</p> <p>GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)</p> <p>vs</p> <p>non-GLP-1 receptor based therapies</p>	<p>MA (RCTs)</p> <p>Type 2 diabetics ≥18 years of age</p>	<p>N=not reported</p> <p>8 to 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change</p> <p>Secondary: Health-related quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function</p>	<p>Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).</p> <p>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)				<p>to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI, -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78).</p> <p>Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).</p> <p>Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92).</p> <p>Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).</p> <p>Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).</p> <p>Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).</p> <p>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).</p> <p>Patients receiving liraglutide 1.8 mg experienced a significant weight loss</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).</p> <p>Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).</p> <p>Secondary: Data on mortality and morbidity were not reported for any treatment.</p> <p>Quality of life Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.</p> <p>Data for liraglutide were not reported.</p> <p>Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).</p> <p>Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.</p> <p>BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported.</p> <p>Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported.</p> <p>FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).</p> <p>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported).</p> <p>PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).</p> <p>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable.</p> <p>Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.</p> <p>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported.</p> <p>β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.</p>
Gangji et al. ¹⁷³ (2007) Glyburide	MA (21 trials) Patients with type 2 diabetes	N=not reported Duration varied	Primary: Hypoglycemia, glycemic control, cardiovascular events, body	Primary: Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52; 95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sulfonylureas, meglitinides, insulin			weight, death Secondary: Not reported	Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues. Secondary: Not reported
Lincoff et al. ¹⁷⁴ (2007) Pioglitazone monotherapy vs metformin (1 trial), placebo (4 trials), sulfonylureas (6 trials) or rosiglitazone (1 trial) or pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo	DB, MA, RCT with placebo or active comparator Adult patients with type 2 diabetes and inadequate glycemic control	N=16,390 (19 trials) 4 months to 3.5 years	Primary: Composite of death from any cause, MI or stroke Secondary: Incidence of serious heart failure	Primary: Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09). Progressive separation of time-to-event curves became apparent after approximately one year of therapy. Secondary: Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).
Karter et al. ¹⁷⁵ (2005) Patients initiated pioglitazone (15.2%), sulfonylureas	Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente	N=23,440 10.2 months (mean)	Primary: Time-to-incident admission to hospital for congestive heart failure	Primary: Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies	Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001		Secondary: Not reported	95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99). Secondary: Not reported
Nissen et al. ¹⁷⁶ (2007) Rosiglitazone monotherapy or combination therapy vs placebo or active comparators (including gliclazide*, glimepiride, glipizide, glyburide, insulin, and metformin)	MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and DREAM trials) Mean age of participants was 56 years, mean baseline HbA _{1c} 8.2%	42 trials n=15,560 for rosiglitazone; n=12,283 for comparator 24 to 208 weeks	Primary: MI and death from cardiovascular causes Secondary: Not reported	Primary: Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03). Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06). Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24). Secondary: Not reported
Kheirbek et al. ¹⁷⁷ (2013) Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride,	OS, RETRO Veterans with diabetes cared for at a Veterans Administration Capital area medical center	N=17,773 Variable duration	Primary: All-cause mortality Secondary: Not reported	Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use</p>				<p>statistically significant increased mortality after controlling for possible drug interactions.</p> <p>Secondary: Not reported</p>
<p>Mearns et al.¹⁷⁸ (2015)</p> <p>Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)</p>	<p>Network MA (62 RCTs)</p> <p>Patients with inadequately controlled type 2 diabetes on metformin alone</p>	<p>N=32,185</p> <p>3 to 12 months</p>	<p>Primary: Changes in HbA_{1c}, body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection</p> <p>Secondary: Not reported</p>	<p>Primary: All agents significantly reduced HbA_{1c} vs placebo; although, not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03).</p> <p>Secondary: Not reported</p>
Long-Term Outcomes Trials				
<p>DCCT Research Group¹⁷⁹ (1993)</p> <p>Insulin administered QD or BID</p>	<p>RCT</p> <p>Insulin-dependent patients with type 1 diabetes with mild retinopathy (secondary)</p>	<p>N=1,441</p> <p>6.5 years (mean)</p>	<p>Primary: Effect on retinopathy development (primary prevention cohort) or</p>	<p>Primary: Intensive insulin therapy significantly reduced the risk of retinopathy onset (primary prevention cohort) by 76% compared to standard therapy (P<0.001).</p> <p>Intensive insulin therapy significantly reduced the risk of retinopathy progression (secondary prevention cohort) by 54% compared to standard</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>insulin administered TID or via external pump</p>	<p>prevention cohort) or without retinopathy (primary prevention cohort), baseline HbA_{1c} 9.1% in both treatment groups</p>		<p>progression (secondary prevention cohort)</p> <p>Secondary: Effect on renal function (micro-albuminuria and albuminuria), neuropathy development, and macrovascular disease</p>	<p>therapy (P<0.001).</p> <p>Secondary: Intensive insulin therapy significantly reduced the risk of microalbuminuria by 34% in the primary prevention cohort (P=0.04) and by 43% in the secondary prevention cohort (P=0.001) compared to standard therapy.</p> <p>Intensive insulin therapy significantly reduced the risk of albuminuria by 56% in the secondary prevention cohort (P=0.01) compared to standard therapy.</p> <p>Intensive insulin therapy significantly reduced the risk of neuropathy appearance by 69% in the primary prevention cohort (P=0.006) and by 57% in the secondary prevention cohort (P<0.001) compared to standard therapy.</p> <p>Nonsignificant reduction of risk of macrovascular disease was observed with intensive insulin therapy (44%; 95% CI, -10 to 68) compared to standard therapy.</p> <p>Intensive insulin therapy had a threefold higher incidence of hypoglycemic events (P<0.001) compared to standard therapy.</p>
<p>UKPDS Group¹⁸⁰ (1998)</p> <p>Intensive therapy with sulfonylurea (chlorpropamide, glyburide, or glipizide) or insulin</p> <p>vs</p> <p>dietary therapy</p>	<p>RCT</p> <p>Patients newly diagnosed with type 2 diabetes, baseline HbA_{1c} 7.05% in the dietary treatment group and 7.09% in the intensive therapy group</p>	<p>N=3,867</p> <p>10 years</p>	<p>Primary: Time to the first occurrence of any diabetes-related endpoint, time to diabetes-related death, all-cause mortality</p> <p>Secondary: MI, sudden death, stroke, amputation or death due to</p>	<p>Primary: There was a 12% risk reduction (95% CI, 1 to 21; P=0.029) for any diabetes-related end point, 10% risk reduction (95% CI, -11 to 27; P=0.34) for any diabetes-related death, and a 6% risk reduction (95% CI, -10 to 20; P=0.44) for all-cause mortality when intensive therapy (sulfonylurea or insulin) was compared to conventional therapy with diet.</p> <p>Patients receiving an intensive treatment (sulfonylurea or insulin) had a 25% risk reduction (95% CI, 7 to 40; P=0.0099) in microvascular end points compared with conventional therapy with diet. Most of this reduction was due to fewer cases of retinal photocoagulation.</p> <p>There were no differences between the intensive and conventional treatment groups or between the three intensive treatment groups in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			peripheral vascular disease, microvascular complications, retinopathy, vitreous hemorrhage, and/or fatal or nonfatal renal failure	<p>number of patients who had a silent MI, cardiomegaly, evidence of peripheral vascular disease, or absent peripheral pulses.</p> <p>Secondary: There was no significant difference between chlorpropamide, insulin, and glibenclamide in macrovascular events.</p> <p>There was no significant difference between the three intensive treatments in microvascular end points or in the risk reduction for retinal photocoagulation.</p>

*Agent is not available in the United States.

†Glibenclamide is a synonym for glyburide.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, TID=three times daily, QID=four times daily

Study abbreviations: AC=active-comparator, CS=comparator study, ES=extension study, MA=meta-analysis, MC=multicenter, MN=multinational, NI=noninferiority, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, RETRO=retrospective, SR=systematic review, XO=cross-over

Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, CSII=continuous subcutaneous insulin infusion, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HR=hazard ratio, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=human insulin isophane (neutral protamine Hagedorn), OR=odds ratio, PP=per protocol, PPG=post-prandial glucose, REG=regular human insulin, RR=relative risk, SBP=systolic blood pressure, SDS=standard deviation score, SEM=standard error of mean, TC=total cholesterol, TG=triglycerides, TZD=thiazolidinedione, WMD=weighted mean difference

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

Yamada et al. evaluated the effects of switching patients to biphasic insulin lispro. Patients with type 2 diabetes who were receiving biphasic human insulin (70/30 or 50/50 mix) were randomized to continue their regimen or switch to biphasic insulin lispro (50/50 mix). There was a significant improvement in HbA_{1c} following the transition to premixed insulin lispro. This change in therapy did not affect quality of life; however, patients reported an improvement in convenience with biphasic insulin lispro.¹⁸¹ Sharma et al. evaluated the effects of switching patients to a rapid-acting insulin regimen. Patients with poorly controlled type 2 diabetes mellitus on biphasic human insulin were switched to biphasic insulin aspart 30. There was a significant improvement in HbA_{1c}, fasting plasma glucose and postprandial glucose, as well as a reduction in hypoglycemic episodes following the transition to biphasic insulin aspart 30.¹⁸² Yokoyama et al. evaluated the effects of switching patients from basal NPH insulin (administered at bedtime) to insulin glargine (administered in the morning) or continuing their existing NPH insulin therapy. Patients continued on their existing prandial insulin regimen. There was a significant reduction in HbA_{1c} in patients who used insulin glargine compared to patients who continued NPH insulin. The risk of hypoglycemia did not significantly increase with the switch to morning insulin glargine.¹⁸³ Kanazawa et al. evaluated the effects of switching patients with type 1 or type 2 diabetes mellitus to insulin glargine from NPH insulin.¹⁸⁴ After 3 months, HbA_{1c} levels improved significantly after switching to insulin glargine. The frequency of mild-to-moderate hypoglycemia was lower in the insulin glargine group.¹⁸⁴ Dornhorst et al. evaluated the effects of switching patients with type 2 diabetes who were on NPH insulin or insulin glargine to insulin detemir.¹⁸⁵ All patients continued their current oral antidiabetic medications. Glycemic control improved significantly in patients switched to insulin detemir, regardless of their previous therapy with NPH insulin or insulin glargine. The incidence of total and nocturnal hypoglycemic episodes were reduced in patients who were switched from NPH insulin (P<0.0001) or insulin glargine (P<0.01 and P<0.05, respectively) to insulin detemir. The incidence of major hypoglycemic events did not differ significantly from baseline. Mean body weight was also significantly reduced in patients who were switched from NPH insulin (P<0.01) or insulin glargine (P<0.05) to insulin detemir.¹⁸⁵

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 9. Relative Cost of the Insulins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Rapid-Acting Insulins				
Insulin aspart	injection	NovoLog®	\$\$\$\$\$	N/A
Insulin glulisine	injection	Apidra®, Apidra Solostar®	\$\$\$\$\$	N/A
Insulin lispro	injection	Humalog®	\$\$\$\$\$	N/A
Short-Acting Insulins				
Insulin regular, human	inhalation, injection	Afrezza®, Humulin®‡ R, Novolin®‡ R	\$\$\$\$\$	N/A
Intermediate-Acting Insulins				
NPH, human insulin isophane	injection	Humulin®‡ N, Novolin®‡ N	\$\$\$\$\$	N/A
Long-Acting Insulins				
Insulin degludec	injection	Tresiba®	\$\$\$\$\$	N/A
Insulin detemir	injection	Levemir®	\$\$\$\$\$	N/A
Insulin glargine, human recombinant analog	injection	Lantus®, Lantus Solostar®, Toujeo®	\$\$\$\$\$	N/A
Combination Insulins (Intermediate-Acting and Rapid-Acting)				
Insulin aspart protamine and insulin aspart	injection	NovoLog® Mix 70/30	\$\$\$\$\$	N/A
Insulin lispro protamine and insulin lispro	injection	Humalog® Mix 50/50, Humalog® Mix 75/25	\$\$\$\$\$	N/A
Combination Insulins (Intermediate-Acting and Short-Acting)				
NPH, human insulin isophane and insulin regular, human	injection	Humulin®‡ 70/30, Novolin®‡ 70/30	\$\$\$\$\$	N/A

‡Product is available over-the-counter.
N/A=Not available

X. Conclusions

The insulins have been shown to improve glycemic control in adults and children with diabetes mellitus. There are two types of insulin preparations currently available: human insulin and insulin analogs. They are categorized based on their duration of action, which includes rapid-acting, short-acting, intermediate-acting, and long-acting insulins. There are no generic products available; however, some insulins are available over-the-counter.

According to current clinical guidelines regarding the management of type 1 diabetes, initiation of individualized, intensive insulin therapy at the time of diagnosis is recommended. Furthermore, overall approaches for management include the use of multiple dose injections or a subcutaneous insulin infusion, and matching of pre-prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. According to the American Diabetes Association, insulin analogs should be utilized in most patients. In addition, use of a continuous subcutaneous insulin infusion is indicated in certain clinical settings, particularly when glycemic control is difficult to achieve, during pregnancy, or when the patient does not demonstrate a willingness to comply with a multiple injection regimen. As mentioned previously, insulin regimens should be tailored to the specific clinical circumstances in individual patients, and patients should have access to the types (preparation and species) of insulin therapy they find allow them optimal well-being. In general, pre-prandial rapid-acting insulin analogs should be administered 20 to 30 minutes prior to a meal. Regular insulin might be considered, instead of rapid-acting, to obtain better control of post-prandial and premeal glucose levels in patients with gastroparesis. Some patients treated with basal, or long-acting, insulin may require twice-daily dosing to achieve greater control. Basal insulin should be provided by the use of isophane (NPH) or long-acting insulin analogs. Use of long-acting analogs should occur when nocturnal hypoglycemia is a problem with NPH, when morning hypoglycemia on NPH results in difficult daytime blood glucose control, or when rapid-acting insulin analogs are used for mealtime blood glucose control. Use of biphasic rapid-acting analog mixes (i.e., combination insulins) may be advantageous in patients prone to hypoglycemia at night. In general, no one specific insulin product among the various classifications is recommended or preferred over another. Again, insulin therapy must be individualized as the products within the different classifications play specific roles in achieving adequate glycemic control in patients

with type 1 diabetes. Insulin therapy may also be appropriate in the management of type 2 diabetes; however, traditionally oral antidiabetic agents are utilized. Of note, many patients with type 2 diabetes will ultimately require insulin therapy, alone or in combination with other agents, to maintain glucose control. Insulin is recognized as a potential option to be added to current oral antidiabetic agent regimens in patients not achieving glycemic goals. It may also be appropriate to initiate insulin therapy at the time of diagnosis in certain clinical settings, particularly in patients with a high baseline glycosylated hemoglobin (HbA_{1c}) ($\geq 9.0\%$), or in patients presenting with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c}. Furthermore, such therapy is mandatory when catabolic features are exhibited or if ketonuria is demonstrated.²¹⁻³³

Numerous clinical trials have established the efficacy/safety of insulin therapy as monotherapy, as well as in combination with other antidiabetic agents.³⁴⁻¹⁸⁰ For the treatment of type 1 diabetes mellitus, several studies have compared the efficacy and safety of prandial insulin regimens, while maintaining stable basal insulin regimens. The use of rapid-acting insulin analogs has resulted in a similar, or greater, reduction in HbA_{1c} compared to regular insulin. The rate of hypoglycemia was found to be either similar, or lower, with the rapid-acting insulin analogs compared to regular insulin.^{34-37,41,43} Head-to-head trials of rapid-acting analogs suggest comparable effectiveness in terms of decreasing HbA_{1c}, achieving similar self-monitored glucose profiles, rates of hyperglycemia, and achieving glycemic goals in type 1 diabetics.³⁸⁻⁴⁰ Other trials have evaluated the efficacy and safety of various basal insulin regimens, while maintaining stable prandial insulin regimens. The use of long-acting insulin analogs has resulted in a similar, or greater, reduction in HbA_{1c} compared to NPH insulin. The rate of hypoglycemia was found to be either similar, or lower, with the long-acting insulin analogs compared to NPH insulin.^{68,70-80,82,85,88,90,92} Two trials directly compared insulin detemir and insulin glargine as basal therapy, while maintaining stable therapy with insulin aspart. There was a similar reduction in HbA_{1c} reported in both studies and the overall rates of hypoglycemia did not differ among the treatment groups. However, nocturnal hypoglycemia was significantly lower with insulin detemir (reported in only one study).^{68,69} Two studies compared insulin aspart and insulin lispro administered through a continuous subcutaneous insulin infusion. There was no difference in HbA_{1c} at the end of the 16-week trials and the rates of hypoglycemia were similar among the treatment groups.^{46,47}

For the treatment of type 2 diabetes mellitus, several studies have compared the efficacy and safety of insulin therapy alone, or in combination with oral antidiabetic drugs. The use of rapid-acting insulin analogs has resulted in a similar, or greater, reduction in HbA_{1c} compared to regular insulin. There was no difference in hypoglycemic episodes reported among the treatment groups.^{50,52,53,59,60} The majority of the studies comparing long-acting insulin analogs to NPH insulin have demonstrated similar reductions in HbA_{1c}.^{108-110,112,120-122,125-127} However, the long-acting insulin analogs were associated with less hypoglycemia than NPH insulin.^{109,110,112,120-127} Two studies directly compared insulin detemir with insulin glargine and showed no difference in HbA_{1c} after 52 weeks of treatment.^{102,104} A third study reported a greater reduction in HbA_{1c} with insulin glargine than insulin detemir after 26 weeks of therapy (-1.28% vs -1.08%, respectively; $P=0.035$); however, the difference between the two treatments (0.207%) was not clinically meaningful.¹⁰³ An additional study also found a greater reduction in HbA_{1c} with insulin glargine than insulin detemir, but did not establish significance.¹⁰⁶ There was no difference in the risk of overall hypoglycemia in any of the studies.¹⁰²⁻¹⁰⁴ In a study comparing biphasic insulin lispro (75/25 mix) and biphasic insulin aspart (70/30 mix), there was no significant difference in HbA_{1c} or overall hypoglycemia reported among the treatment groups.⁵¹

The approval of Tresiba[®] (insulin degludec) was based on FDA review of the BEGIN clinical trial program, which was comprised of a series of phase III studies evaluating the efficacy and safety of this agent in adults with type 1 and 2 diabetes. In this clinical trial program, this agent was generally found to be non-inferior to Lantus[®] (insulin glargine) and associated with a similar side effect profile.^{19,65-67,94,98,100} In the EDITION clinical trial program, Toujeo[®] (insulin glargine) was demonstrated to be non-inferior to Lantus[®] (insulin glargine) in measures of glycemic control in patients with type 1 and 2 diabetes.^{20,89,133-116} In all studies, a higher dose of Toujeo[®] (insulin glargine) compared to Lantus[®] (insulin glargine) was required to achieve comparable glucose control. This was thought to be due to the pharmacokinetic profile, specifically the release of the drug from the subcutaneous depot.^{20,89,133-116} In clinical trials, Afrezza[®] (insulin human, regular) has been studied in type 1 and 2 diabetes and demonstrated efficacy compared to placebo.^{18,55,56} However, in patients with type 1 diabetes specifically, although Afrezza[®] met the non-inferiority margin, the agent provided statistically lower reductions in HbA_{1c} compared to mealtime dosing of insulin aspart.¹⁸ Afrezza[®] has a similar adverse event profile as other agents; however it does have a boxed warning for pulmonary reactions included acute bronchospasm and is contraindicated in patients with chronic lung disease.¹⁸

In summary, the insulin analogs have been shown to be at least as effective, or more effective, than human insulin. In several studies, there was a lower risk of hypoglycemia with the insulin analogs compared to human insulin. There is insufficient evidence to conclude that one rapid-acting insulin analog is safer or more efficacious than another. There is also insufficient evidence to conclude that one long-acting insulin analog is safer or more efficacious than another.

Therefore, all brand products within the class reviewed, with the exception of rapid-acting and long-acting insulin analogs, are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Rapid-acting insulin analogs offer significant clinical advantages in general use over short-acting human insulin, but are comparable to each other. Long-acting insulin analogs offer significant clinical advantages in general use over intermediate-acting human insulin, but are comparable to each other.

XI. Recommendations

No brand insulin, with the exception of rapid-acting and long-acting insulin analogs, is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand rapid-acting insulin analog is selected as a preferred agent.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand long-acting insulin analog is selected as a preferred agent.

XII. References

1. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2017 Feb]. Available from: <http://www.thomsonhc.com/>.
2. Facts and Comparisons[®] eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Feb 2017]. Available from: <http://online.factsandcomparisons.com>.
3. Apidra[®] [package insert]. Bridgewater (NJ): sanofi-aventis U.S. LLC; 2015 Feb.
4. Humalog[®] [package insert]. Indianapolis (IN): Eli Lilly and Company; 2015 May.
5. Humulin[®] N [package insert]. Indianapolis (IN): Eli Lilly and Company; 2015 Feb.
6. Humulin[®] R [package insert]. Indianapolis (IN): Eli Lilly and Company; 2015 Feb.
7. Humulin[®] R U-500 [package insert]. Indianapolis (IN): Eli Lilly and Company; 2015 Dec.
8. Novolin[®] N [package insert]. Plainsboro (NJ): Novo Nordisk Inc.; 2016 Jan.
9. Novolin[®] R [package insert]. Plainsboro (NJ): Novo Nordisk Inc.; 2016 Jan.
10. NovoLog[®] [package insert]. Plainsboro (NJ): Novo Nordisk Inc.; 2015 Feb.
11. Humalog[®] Mix 50/50 [package insert]. Indianapolis (IN): Eli Lilly and Company; 2015 Feb.
12. Humalog[®] Mix 75/25 [package insert]. Indianapolis (IN): Eli Lilly and Company; 2015 Feb.
13. Humulin[®] 70/30 [package insert]. Indianapolis (IN): Eli Lilly and Company; 2015 Feb.
14. Lantus[®] [package insert]. Bridgewater (NJ): sanofi-aventis U.S. LLC; 2015 Jul.
15. Levemir[®] [package insert]. Plainsboro (NJ): Novo Nordisk Inc.; 2015 Feb.
16. Novolin[®] 70/30 [package insert]. Plainsboro (NJ): Novo Nordisk Inc.; 2016 Jan.
17. NovoLog[®] Mix 70/30 [package insert]. Plainsboro (NJ): Novo Nordisk Inc.; 2015 Feb.
18. Afrezza[®] [package insert]. Bridgewater (NJ): sanofi-aventis U.S. LLC; 2015 May.
19. Tresiba[®] [package insert]. Plainsboro (NJ): Novo Nordisk Inc.; 2016 Dec.
20. Toujeo[®] [package insert]. Bridgewater (NJ): sanofi-aventis U.S. LLC; 2015 Feb.
21. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* 2016;39(Suppl. 1):S1–S112.
22. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012 Jun;35(6):1364-79.
23. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2015 Mar;58(3):429-42.
24. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2012 Feb 7;156(3):218-31.
25. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract*. 2015 Apr;21 Suppl 1:1-87.
26. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. *Endocr Pract*. 2016;22(1):84-113.
27. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
28. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. *Diagnosis and Management of Type 2 Diabetes Mellitus in Adults*. Updated July 2014.
29. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
30. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. *Pediatrics* 2013;131(2):364-382.
31. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.

32. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.
33. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. *Diabetes Care* 2014;37(7):2034-2054.
- Home PD, Hallgren P, Usadel KH, Sane T, Faber J, Grill V, et al. Pre-meal insulin aspart compared with pre-meal soluble human insulin in type 1 diabetes. *Diabetes Clin Res Pract*. 2006 Feb;71(2):131-9.
34. Home PD, Hallgren P, Usadel KH, Sane T, Faber J, Grill V, et al. Pre-meal insulin aspart compared with pre-meal soluble human insulin in type 1 diabetes. *Diabetes Clin Res Pract*. 2006 Feb;71(2):131-9.
35. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care*. 2000;23(5):583-8.
36. Mathiesen ER, Kinsley B, Amiel SA, Heller S, McCance D, Duran S, et al. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy. *Diabetes Care*. 2007 Apr;30(4):771-6.
37. Garg SK, Rosenstock J, Ways K. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with Basal insulin glargine. *Endocr Pract*. 2005;11(1):11-7.
38. Dreyer M, Prager R, Robinson A, Busch K, Ellis G, Souhami E, et al. Efficacy and safety of insulin glulisine in patients with type 1 diabetes. *Horm Metab Res*. 2005;37(11):702-7.
39. Philotheou A, Arslanian S, Blatniczky L, Peterkova V, Souhami E, Danne T. Comparable efficacy and safety of insulin glulisine and insulin lispro when given as part of a Basal-bolus insulin regimen in a 26-week trial in pediatric patients with type 1 diabetes. *Diabetes Technol Ther*. 2011 Mar;13(3):327-34.
40. van Ban AC, Bode BW, Sert-Langeron C, DeVries JH, Charpentier G. Insulin glulisine compared to insulin aspart and to insulin lispro administered by continuous subcutaneous insulin infusion in patients with type 1 diabetes: a randomized controlled trial. *Diabetes Technol Ther*. 2011 Jun;13(6):607-14.
41. Rave K, Klein O, Frick AD, Becker RHA. Advantage of premeal-injected insulin glulisine compared with regular human insulin in subjects with type 1 diabetes. *Diabetes Care*. 2006 Aug;29(8):1812-7.
42. Anderson JH Jr, Brunelle RL, Koivisto VA, Pfofzner A, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. *Diabetes*. 1997;46(2):265-70.
43. Fairchild JM, Amber GR, Genoud-Lawton CH, Westman EA, Chan A, Howard NJ, et al. Insulin lispro versus regular insulin in children with type 1 diabetes on twice daily insulin. *Pediatr Diabetes*. 2000 Sep;1(3):135-41.
44. Mortensen H, Kocova M, Teng LY, Keiding J, Bruckner I, Philotheou A. Biphasic insulin aspart vs human insulin in adolescents with type 1 diabetes on multiple daily insulin injections. *Pediatr Diabetes*. 2006 Feb;7(1):4-10.
45. Chen JW, Lauritzen T, Bojesen A, Christiansen JS. Multiple mealtime administration of biphasic insulin aspart 30 versus traditional basal-bolus human insulin treatment in patients with type 1 diabetes. *Diabetes Obes Metab*. 2006 Nov;8(6):682-9.
46. Bode B, Weinstein R, Bell D, et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: A randomized study in type 1 diabetes. *Diabetes Care* 2002;25:439-444.
47. Weinzimer SA, Ternand C, Howard C, et al. A randomized trial comparing continuous subcutaneous insulin infusion of insulin aspart versus insulin lispro in children and adolescents with type 1 diabetes. *Diabetes Care* 2008;31:210-5.
48. Colquitt J, Royle P, Waugh N. Are analogue insulins better than soluble in continuous subcutaneous insulin infusion? Results of a meta-analysis. *Diabet Med*. 2003;20(10):863-6.
49. McSorley PT, Bell PM, Jacobsen LV, Kristensen A, Lindholm A. Twice-daily biphasic insulin aspart 30 versus biphasic human insulin 30: a double-blind crossover study in adults with type 2 diabetes mellitus. *Clin Ther*. 2002 Apr;24(4):530-9.
50. Bretzel RG, Arnolds S, Medding J, Linn T. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. *Diabetes Care*. 2004 May;27(5):1023-7.
51. Niskanen L, Jensen LE, Rastam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. *Clin Ther*. 2004;26(4):531-40.
52. Dailey G, Rosenstock J, Moses RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2004;27(10):2363-8.

53. Rayman G, Profozic V, Middle M. Insulin glulisine imparts effective glycaemic control in patients with type 2 diabetes. *Diabetes Res Clin Pract.* 2007;76:304-12.
54. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes, previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) vs basal/bolus (glargine/lispro) therapy. *Diabetes Care.* 2008 Jan;31(1):20-5.
55. Tack CJ, Christov V, de Galan BE *et al.* Randomized forced titration to different doses of Technosphere® Insulin demonstrates reduction in postprandial glucose excursions and hemoglobin A1c in patients with type 2 diabetes. *J Diabetes Sci Technol* 2008; 2: 47–57.
56. Rosenstock J, Bergenstal R, DeFronzo RA, et al. Efficacy and safety of Technosphere inhaled insulin compared with Technosphere powder placebo in insulin-naïve type 2 diabetes suboptimally controlled with oral agents. *Diabetes Care.* 2008 Nov;31(11):2177-82.
57. Rosenstock J, Lorber DL, Gnudi L *et al.* Prandial inhaled insulin plus basal insulin glargine versus twice daily biapart insulin for type 2 diabetes: a multicentre randomised trial. *Lancet* 2010; 375: 2244–2253.
58. Raskin P, Heller S, Honka M, et al. Pulmonary function over 2 years in diabetic patients treated with prandial inhaled Technosphere Insulin or usual antidiabetes treatment: a randomized trial. *Diabetes Obes Metab.* 2012 Feb;14(2):163-73.
59. Vignati L, Anderson JH Jr, Iversen PW. Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. *Clin Ther.* 1997;19(6):1408-21.
60. Anderson JH Jr, Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. *Clin Ther.* 1997;19(1):62-72.
61. Plank J, Siebenhofer A, Berghold A, Jeitler K, et al. Systematic review and meta-analysis of short-acting insulin analogs in patients with diabetes mellitus. *Arch Intern Med.* 2005;165(12):1337-44.
62. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, et al. Short-acting insulin analogs versus regular human insulin in patients with diabetes mellitus (review). *Cochrane Database Syst Rev.* 2006 Apr 19;(2):CD003287.
63. Thalange N, Deeb L, Iotova V, et al. Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes. *Pediatr Diabetes.* 2015 May;16(3):164-76.
64. Davies M, Sasaki T, Gross JL, et al. Comparison of insulin degludec with insulin detemir in type 1 diabetes: a 1-year treat-to-target trial. *Diabetes Obes Metab.* 2016 Jan;18(1):96-9.
65. Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet.* 2012 Apr 21;379(9825):1489-97.
66. Bode BW, Buse JB, Fisher M, Garg SK, Marre M, Merker L et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN® Basal-Bolus Type 1): 2-year results of a randomized clinical trial. *Diabet Med.* 2013 Nov;30(11):1293-7. doi: 10.1111/dme.12243.
67. Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, Russell-Jones D et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. *J Clin Endocrinol Metab.* 2013 Mar;98(3):1154-62. doi: 10.1210/jc.2012-3249.
68. Pieber TR, Treichel HC, Hompesch B, Philotheou A, Mordhorst L, Gall MA, et al. Comparison of insulin detemir and insulin glargine in subjects with type 1 diabetes using intensive insulin therapy. *Diabet Med.* 2007 Jun;24(6):635-42.
69. Heller S, Koenen C, Bode B, et al. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. *Clin Ther* 2009;31:2086-97.
70. Vague P, Selam JL, Skeie S, De Leeuw I, Elte JW, Haahr H, Kristensen A, Draeger E. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care.* 2003; 26(3):590-6.
71. Hermansen K, Fontaine P, Kukulja KK, Peterkova V, Leth G, Gall MA. Insulin analogs (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia.* 2004;47(4):622-9.

72. Home P, Bartley P, Russell-Jones D, Hanaire-BROUTIN H, Heeg JE, Abrams P, et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes. *Diabetes Care*. 2004 May;27(5):1081-7.
73. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus regimen. *Clin Ther*. 2004 May;26(5):724-36.
74. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. *Diabetes Technol Ther*. 2004;6(5):579-88.
75. De Leeuw I, Vague P, Selam JL, Skeie S, Lang H, Draeger E, Elte JW. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obes Metab*. 2005;7(1):73-82.
76. Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three multiple injection regimens for type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs morning plus bedtime NPH insulin. *Diabet Med*. 2005;22(7):850-7.
77. Kølendorf K, Ross GP, Pavlic-Renar I, Perriello G, et al. Insulin detemir lowers the risk of hypoglycemia and provides more consistent plasma glucose levels compared with NPH insulin in Type 1 diabetes. *Diabet Med*. 2006;23(7):729-35.
78. Robertson KJ, Schoenle E, Gucev Z, Mordhorst L, Gall MA, Ludvigsson J. Insulin detemir compared with NPH insulin in children and adolescents with type 1 diabetes. *Diabet Med*. 2007;24:27-34.
79. Bartley PC, Bogoev M, Larsen J, et al. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. *Diabet Med* 2008;25:442-9.
80. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care*. 2000;23(5):639-43.
81. Tan CY, Wilson DM, Buckingham B. Initiation of insulin glargine in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2004 Jun;5(2):80-6.
82. Ashwell SG, Amiel SA, Biloust RW, Dashora U, Heller SR, Hepburn DA, et al. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with type 1 diabetes. *Diabet Med*. 2006 Mar;23(3):285-92.
83. Herwig J, Scholl-Schilling G, Böhles H. Glycaemic control and hypoglycaemia in children, adolescents and young adults with unstable type 1 diabetes mellitus treated with insulin glargine or intermediate-acting insulin. *J Pediatr Endocrinol Metab*. 2007 Apr;20(4):517-25.
84. Kudva YC, Basu A, Jenkins GD, Pons GM, Vogelsang DA, Rizza RA, et al. Glycemic variation and hypoglycemia inpatients with well-controlled type 1 diabetes on a multiple daily insulin injection program with use of glargine and Ultralente as basal insulin. *Endocr Pract*. 2007 May-Jun;13(3):244-50.
85. Chatterjee S, Jarvis-Kay J, Rengarajan T, Lawrence IG, McNally PG, Davies MJ. Glargine versus NPH insulin: efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes-the glargine and aspart study (GLASS) a randomized cross-over study. *Diabetes Res Clin Pract*. 2007 Aug;77(2):215-22.
86. Manini R, Forlani G, Moscatiello S, Zannoni C, Marzocchi R, Marchesini G. Insulin glargine improves glycemic control and health-related quality of life in type 1 diabetes. *Nutr Metab Cardiovasc Dis*. 2007 Sept;17(7):493-8.
87. Rosenstock J, Park G, Simmerman J. Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. *Diabetes Care*. 2000 Aug;23(8):1137-42.
88. Rossetti P, Pampanelli S, Fanelli C, Porcellati F, Costa E, Torlone E, et al. Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime. *Diabetes Care*. 2003 Mar;26(5):1490-6.
89. Home PD, Bergenstal RM, Bolli GB, et al. New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4). *Diabetes Care*. 2015 Dec;38(12):2217-25.
90. Pesić M, Zivić S, Radenković S, Velojić M, Dimić D, Antić S. Comparison between basal insulin glargine and NPH insulin in patients with diabetes type 1 on conventional intensive insulin therapy. *Vojnosanit Pregl*. 2007 April;64(4):247-52.
91. Dundar BN, Dundar N, Eren E. Comparison of the efficacy and safety of insulin glargine and insulin detemir with NPH insulin in children and adolescents with type 1 diabetes mellitus receiving intensive insulin therapy. *J Clin Res Pediatr Endocrinol*. 2009;1(4):181-7.

92. Chase HP, Arslanian S, White NH, et al. Insulin glargine versus intermediate-acting insulin as the basal component of multiple daily injection regimens for adolescents with type 1 diabetes mellitus. *J Pediatr* 2008;153:547-53.
93. Ahern JAH, Boland EA, Doane R, Ahern JJ, Rose P, Vincent M, et al. Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower A1C levels across all age groups. *Pediatr Diabetes*. 2002 Mar;3(1):10-5.
94. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care*. 2012 Dec;35(12):2464-71. doi: 10.2337/dc12-1205.
95. Rodbard HW, Cariou B, Zinman B, Handelsman Y, Philis-Tsimikas A, Skjøth TV et al. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. *Diabet Med*. 2013 Nov;30(11):1298-304. doi: 10.1111/dme.12303.
96. Philis-Tsimikas A, Del Prato S, Satman I, Bhargava A, Dharmalingam M, Skjøth TV et al. Effect of insulin degludec versus sitagliptin in patients with type 2 diabetes uncontrolled on oral antidiabetic agents. *Diabetes Obes Metab*. 2013 Aug;15(8):760-6. doi: 10.1111/dom.12115.
97. Meneghini L, Atkin SL, Gough SC, Raz I, Blonde L, Shestakova M et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes Care*. 2013 Apr;36(4):858-64. doi: 10.2337/dc12-1668.
98. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Muñoz-Torres M et al. Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012 Apr 21;379(9825):1498-507.
99. Hollander P, King AB, Del Prato S, Sreenan S, Balci MK, Muñoz-Torres M et al. Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy. *Diabetes Obes Metab*. 2015 Feb;17(2):202-6. doi: 10.1111/dom.12411.
100. Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycaemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes Care*. 2013 Sep;36(9):2536-42. doi: 10.2337/dc12-2329.
101. Meneghini LF, Rosenberg KH, Koenen C, Merilainen MJ, Lükkeke HJ. Insulin detemir improves glycaemic control with less hypoglycemia and no weight gain in patients with type 2 diabetes who were insulin naïve or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. *Diabetes Obes Metab*. 2007 May;9(3):418-27.
102. Hollander P, Cooper J, Bregnhøj J, et al. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clin Ther* 2008;30:1976-87.
103. Raskin P, Gylvin T, Weng W, et al. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes Metab Res Rev* 2009;25:542-8.
104. Rosenstock J, Davies M, Home PD, et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008;51:408-16.
105. King AB. Once-daily insulin detemir is comparable to once-daily insulin glargine in providing glycaemic control over 24 hour in patients with type 2 diabetes: a double-blind, randomized, crossover study. *Diabetes Obes Metab*. 2009 Jan;11(1):69-71.
106. Meneghini L, Kesavadev J, Demissie M, Nazeri A, and Hollander P. Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. *Diabetes Obes Metab* 2013;15(8):729-736.
107. Liebl A, Prager R, Binz K, et al. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. *Diabetes Obes Metab* 2009;11:45-52.
108. Haak T, Tiengo A, Draeger E, Suntaum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab*. 2005 Jan;7(1):56-64.
109. Fajardo Montañana C, Hernández Herrero C, Rivas Fernández M. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight Type 2 diabetes patients: the PREDICTIVE BMI clinical trial. *Diabet Med* 2008;25:916-23.

110. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther*. 2006 Oct;28(10):1569-81.
111. Montanana CF, Herrero CH, Fernandez MR. Less weight gain and hypoglycemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight type 2 diabetes patients-the PREDICTIVE BMI clinical trial. *Diabet Med*. 2008;25:916-23.
112. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care*. 2006;29(6):1269-74.
113. Riddle MC, Bolli GB, Ziemien M, Muehlen-Bartmer I, Bizet F, Home PD, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care*. 2014 Oct;37(10):2755-62. doi: 10.2337/dc14-0991. Epub 2014 Jul 30.
114. Yki-Järvinen H, Bergenstal R, Ziemien M, Wardecki M, Muehlen-Bartmer I, Boelle E, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care*. 2014 Dec;37(12):3235-43. doi: 10.2337/dc14-0990. Epub 2014 Sep 5.
115. Bolli GB, Riddle MC, Bergenstal RM, Ziemien M, Sestakauskas K, Goyeau H, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab*. 2015 Apr;17(4):386-94. doi: 10.1111/dom.12438. Epub 2015 Feb 12.
116. Ritzel R, Roussel R, Bolli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab*. 2015 Sep;17(9):859-67.
117. Strojek K, Bebakar WM, Khutsoane DT, Pesic M, Smahelová A, Thomsen HF, et al. Once-daily initiation with biphasic insulin aspart 30 vs insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: an open-label, multinational RCT. *Curr Med Res Opin*. 2009 Dec;25(12):2887-94.
118. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine vs thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycemic agents (APOLLO): an open randomized controlled trial. *Lancet*. 2008 Mar 29;371(9618):1073-84.
119. Buse JB, Wolffenbutter BHR, Herman WH, Shemonsky NK, Jiang HH, Fahrback JL, et al. DURAbility of basal vs lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results. *Diabetes Care*. 2009;32:1007-13.
120. Yki-Järvinen H, Dressler A, Ziemien M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care*. 2000 Aug;23(8):1130-6.
121. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003 Nov;26(11):3080-6.
122. Rosenstock J, Fonseca V, McGill JB, et al. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. *Diabetologia* 2009;52:1778-88.
123. Aschner P, Sethi B, Gomez-Peralta F, et al. Insulin glargine compared with premixed insulin for management of insulin-naïve type 2 diabetes patients uncontrolled on oral antidiabetic drugs: the open-label, randomized GALAPAGOS study. *J Diabetes Complications*. 2015 Aug;29(6):838-45.
124. Fritsche A, Schweitzer MA, Häring HU. Glimepiride combined with morning insulin glargine, bedtime neutral protamine Hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. *Ann Intern Med*. 2003 Jun;138(12):952-9.
125. Pan CY, Sinnassamy P, Chung KD, Kim KW; LEAD Study Investigators Group. Insulin glargine versus NPH insulin therapy in Asian type 2 diabetes patients. *Diabetes Res Clin Pract*. 2007 Apr;76(1):111-8.
126. Eliaschewitz FG, Calvo C, Valbuena H, Ruiz M, Aschner P, Villena J, et al; HOE 901/4013 LA Study Group. Therapy in type 2 diabetes: insulin glargine vs NPH insulin both in combination with glimepiride. *Arch Med Res*. 2006 May;37(4):495-501.
127. Yki-Järvinen H, Kauppinen-Mäkelin RK, Tiikkainen M, Vähätalo M, Virtamo H, Nikkilä K, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia*. 2006 Mar;49(3):442-51.
128. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007;357:1716-30.

129. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009;361:1736-47.
130. Garber AJ, Clauson P, Pedersen CB, Kølendorf K. Lower risk of hypoglycemia with insulin detemir than with neutral protamine Hagedorn insulin in older persons with type 2 diabetes: a pooled analysis of phase III trials. *J Am Geriatr Soc.* 2007 Nov;55(11):1735-40.
131. Raslová K, Tamer SC, Clauson P, Karl D. Insulin detemir results in less weight gain than NPH insulin when used in basal-bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. *Clin Drug Investig.* 2007;27(4):279-85.
132. Siegmund T, Weber S, Blankenfeld H, Oeffner A, Schumm-Draeger PM. Comparison of insulin glargine versus NPH insulin in people with type 2 diabetes mellitus under outpatient-clinic conditions for 18 months using a basal-bolus regimen with a rapid-acting insulin analogue as mealtime insulin. *Exp Clin Endocrinol Diabetes.* 2007 Jun;115(6):349-53.
133. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care.* 2005;28(4):950-5.
134. Berard L, Cameron B, Woo V, Stewart J. Replacing Insulin Glargine with Neutral Protamine Hagedorn (NPH) Insulin in a Subpopulation of Study Subjects in the Action to Control Cardiovascular Risk in Diabetes (ACCORD): Effects on Blood Glucose Levels, Hypoglycemia and Patient Satisfaction. *Can J Diabetes.* 2015 Aug;39(4):296-301.
135. Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzner TW, Plank J, et al. Long-acting insulin analogs versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Sys Rev.* 2007 Apr 18;(2):CD005613.
136. Bazzano LA, Lee LJ, Shi L, et al. Safety and efficacy of glargine compared with NPH insulin for the treatment of Type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabet Med* 2008;25:924-32.
137. Davidson JA, Liebl A, Christiansen JS, et al. Risk for nocturnal hypoglycemia with biphasic insulin aspart 30 compared with biphasic human insulin 30 in adults with type 2 diabetes mellitus: a meta-analysis. *Clin Ther* 2009;31:1641-51.
138. Fakhoury W, Lockhart I, Kotchie RW, Aagren M, LeReun C. Indirect comparison of once daily insulin detemir and glargine in reducing weight gain and hypoglycemic episodes when administered in addition to conventional oral anti-diabetic therapy in patients with type-2 diabetes. *Pharmacology.* 2008;82(2):156-63.
139. Singh SR, Ahmad F, Lal A, et al. Efficacy and safety of insulin analogs for the management of diabetes mellitus: a meta-analysis. *CMAJ* 2009;180:385-97.
140. Yenigun M, Honka M. Switching patients from insulin glargine-based basal bolus regimens to a once daily insulin detemir-based basal-bolus regimen: results from a subgroup of the PREDICTIVE study. *Int J Clin Pract.* 2009 Mar;63(3):425-32.
141. Ignaut DA, Schwartz SL, Sarwat S, et al. Comparative device assessments: Humalog KwikPen compared with vial and syringe and FlexPen. *Diabetes Educ* 2009;35:789-98.
142. Korytkowski M, Bell D, Jacobsen C, Suwannasari R, and the FlexPen Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther.* 2003;25(11):2836-48.
143. Mu PW, Chen YM, Lu HY, Wen XQ, Zhang YH, Xie RY, et al. Effects of a combination of oral anti-diabetes drugs with basal insulin therapy on β -cell function and glycaemic control in patients with newly diagnosed type 2 diabetes. *Diabetes Metab Res Rev.* 2012;28:236-40.
144. Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia.* 2014 Dec;57(12):2475-84.
145. Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2). *Diabetes Care.* 2015 Dec;38(12):2241-9.
146. Okerson T, Yan P, Stonehouse A, Brodows R. Effects of exenatide on systolic blood pressure in subjects with type 2 diabetes. *Am J Hypertens.* 2010;23:334-9.
147. Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, et al. Once weekly exenatide compared to insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomized trial. *Lancet.* 2010;375:2234-43.

148. Diamant M, Van Gaal L, Stranks S, Guerci B, MacConell L, Haber H, et al. Safety and efficacy of once-weekly exenatide compared to insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. *Diabetes Care*. 2012;35:683-9.
149. Bergenstal R, Lewin A, Bailey T et al. Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. *Curr Med Res Opin*. 2009;25(1): 65-75.
150. Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. 2005;143(8):559-69.
151. Secnik Boye K, Matza LS, Oglesby A, et al. Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes. *Health Qual Life Outcomes*. 2006;4:80.
152. Nauck MA, Duran S, Kim D. et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia*. 2007;50(2):259-67.
153. Xu W, Bi Y, Sun Z, et al. Comparison of the effects on glycaemic control and β -cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE study). *J Intern Med*. 2015 Jan;277(1):137-50.
154. Hollander P, Sugimoto D, Vlajnic A, Kilo C. Combination therapy with insulin glargine plus metformin but not insulin glargine plus sulfonylurea provides similar glycemic control to triple oral combination therapy in patients with type 2 diabetes uncontrolled with dual oral agent therapy. *J Diabetes Complications*. 2015 Nov-Dec;29(8):1266-71.
155. Kabadi MU, Kabadi U. Efficacy of sulfonylureas with insulin in type 2 diabetes mellitus. *Ann Pharmacother*. 2003;37(11):1572-6.
156. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomized controlled trial. *Diabetologia*. 2009;52:2046-55.
157. Civera M, Merchante A, Salvador M, Sanz J, Martínez I. Safety and efficacy of repaglinide in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes. *Diabetes Res Clin Pract*. 2008 Jan;79(1):42-7.
158. Cesur M, Corapcioglu D, Gursoy A, Gonen S, Ozduman M, Emral R, et al. A comparison of glycemic effects of glimepiride, repaglinide, and insulin glargine in type 2 diabetes mellitus during Ramadan fasting. *Diabetes Res Clin Pract*. 2007 Feb;75(2):141-7.
159. Chisalita SI, Lindström T, Eson Jennersjö P, Paulsson JF, Westermark GT, Olsson AG, Arnqvist HJ. Differential lipid profile and hormonal response in type 2 diabetes by exogenous insulin aspart versus the insulin secretagogue repaglinide, at the same glycemic control. *Acta Diabetol*. 2009 Mar;46(1):35-42. Epub 2008 Sep 6.
160. Meneghini LF, Traylor L, Schwartz SL. Improved glycemic control with insulin glargine versus pioglitazone as add-on therapy to sulfonylurea or metformin in patients with uncontrolled type 2 diabetes mellitus (abstract). *Endocr Pract*. 2010 Jul-Aug;16(4):588-99.
161. Dorkhan M, Frid A, Groop L. Differences in effects of insulin glargine or pioglitazone added to oral anti-diabetic therapy in patients with type 2 diabetes: what to add--insulin glargine or pioglitazone? *Diabetes Res Clin Pract* 2008;82:340-5.
162. Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. *Am J Med*. 2004;15;116(4):230-5.
163. Ligvay I, Legendre J, Kaloyanova P, et al. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? *Diabetes Care* 2009;32:1789-95.
164. Ibrahim MI, Hamdy A, Shafik A, et al. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. *Arch Gynecol Obstet* 2014; 289:959–965.
165. Spaulonci CP, Bernardes LS, Trindade TC, et al. Randomized trial of metformin vs insulin in the management of gestational diabetes. *Am J Obstet Gynecol* 2013;209:34.e1-7.
166. Niromanesh S, Alavi A, Sharbaf FR, et al. Metformin compared with insulin in the management of gestational diabetes mellitus: A randomized clinical trial. *Diabetes Research and Clinical Practice* 2012;98:422-429.
167. Poolsup N, Suksomboon N, Amin M (2014) Efficacy and Safety of Oral Antidiabetic Drugs in Comparison to Insulin in Treating Gestational Diabetes Mellitus: A Meta-Analysis. *PLoS ONE* 2014;9(10): e109985. doi:10.1371/journal.pone.0109985.
168. Nichols GA, Gomez-Caminero A. Weight changes following the initiation of new anti-hyperglycemic therapies. *Diabetes Obes Metab*. 2007 Jan;9(1):96-102.

169. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogs for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2007 Apr 18;(2):CD004654.
170. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005 Jul 20;(3):CD002966.
171. Monami M, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin.* 2011;27 Suppl 3:57-64.
172. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD006423. DOI: 10.1002/14651858.CD006423.pub2.
173. Gangji AS, Cukierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care.* 2007;30(2):389-94.
174. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA.* 2007 Sep 12;298(10):1180-8.
175. Karter AJ, Ahmed AT, Liu J, Moffet HH, Parker MM. Pioglitazone initiation and subsequent hospitalization for congestive heart failure. *Diabetic Med.* 2005 Aug;22:986-93.
176. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356(24):2457-71.
177. Kheirbek RE, Alemi F, Zargoush M. Comparative effectiveness of hypoglycemic medications among veterans. *J Manag Care Pharm.* 2013;19(9):740-44.
178. Mearns ES, Sobieraj DM, White CM, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One.* 2015 Apr 28;10(4):e0125879.
179. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):977-86.
180. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998 Sep 12;352(9131):837-53.
181. Yamada S, Watanabe M, Kitaoka A, Shiono K, Atsuda K, Tsukamoto Y, et al. Switching from premixed human insulin to premixed insulin lispro: a prospective study comparing the effects on glucose control and quality of life. *Intern Med.* 2007;46(18):1513-7.
182. Sharma SK, Min KW, Azar ST. Transferring type 2 diabetes patients with uncontrolled glycaemia from biphasic human insulin to biphasic insulin aspart 30: experiences from the PRESENT study. *Curr Med Res Opin.* 2007 Nov 14 [Epub ahead of print].
183. Yokoyama H, Tada J, Kamikawa F, Kanno S, Yokota U, Kuramitsu M. Efficacy of conversion from bedtime NPH insulin to morning insulin glargine in type 2 diabetic patients on basal-prandial insulin therapy. *Diabetes Res Clin Pract.* 2006 Jul;73(1):35-40.
184. Kanazawa Y, Igarashi Y, Komiya K, Sakurai Y, Shimizu T, Fujitani Y, et al. Long-term efficacy of insulin glargine after switching from NPH insulin as intensive replacement of basal insulin in Japanese diabetes mellitus. Comparison of efficacy between type 1 and type 2 diabetes (JUN-LAN study 1). *Endocr J.* 2007 Nov 14 [Epub ahead of print].
185. Dornhorst A, Lüddecke HJ, Koenen C, Meriläinen M, King A, Robinson A, et al. Transferring to insulin detemir from NPH insulin or insulin glargine in type 2 diabetes patients on basal-only therapy with oral antidiabetic drugs improves glycaemic control and reduces weight gain and risk of hypoglycaemia: 14-week follow-up data from PREDICTIVE. *Diabetes Obes Metab.* 2008 Jan;10(1):75-81.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Meglitinides
AHFS Class 682016
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The meglitinides are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹⁻³ They are short-acting agents that decrease blood glucose concentrations by stimulating insulin secretion. Meglitinides interact with the ATP-dependent potassium channel on pancreatic beta cells.¹⁻⁵ Blockade of the potassium channel leads to depolarization of the beta cell, which opens the calcium channel. The increased calcium influx induces insulin secretion. Insulin release is glucose dependent and diminishes at low glucose concentrations. Both nateglinide and repaglinide are highly tissue selective with low affinity for heart and skeletal muscle.¹⁻²

Repaglinide is also available in combination with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.³⁻⁵

The meglitinides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the agents are available in a generic formulation. This class was last reviewed in February 2015.

Table 1. Meglitinides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Nateglinide	tablet	Starlix®*	nateglinide
Repaglinide	tablet	Prandin®*	Prandin®*, repaglinide
Combination Products			
Repaglinide and metformin	tablet	N/A	repaglinide and metformin

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Meglitinides

Clinical Guideline	Recommendation(s)
American Diabetes Association: Standards of Medical Care in Diabetes	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) $\geq 6.5\%$, or a fasting plasma glucose (FPG) ≥ 126 mg/dL, or a two-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test or

Clinical Guideline	Recommendation(s)
(2016) ⁶	<p>patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥ 200 mg/dL).</p> <p><u>Prevention or delay of type 2 diabetes</u></p> <ul style="list-style-type: none"> • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥ 150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. • Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus. • Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p><u>Glycemic goals in adults</u></p> <ul style="list-style-type: none"> • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is $<7.0\%$. • It may be reasonable for providers to suggest more stringent HbA_{1c} goals ($<6.5\%$) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals ($<8.0\%$) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p><u>Pharmacologic therapy for type 1 diabetes</u></p> <ul style="list-style-type: none"> • Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. • Most patients should use of insulin analogs to reduce hypoglycemia risk. • Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. <p><u>Pharmacologic therapy for type 2 diabetes</u></p> <ul style="list-style-type: none"> • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If the A_{1c} target is not achieved after approximately three months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • <u>Pregestational Diabetes</u> <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1C} <6.5%, to reduce the risk of congenital anomalies. ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. • <u>Gestational Diabetes Mellitus</u> <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. • <u>General Principles for Management of Diabetes in Pregnancy</u> <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. • Due to increased red blood cell turnover, A_{1C} is lower in normal pregnancy than in normal nonpregnant women. The A_{1C} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012 and 2015 Update)^{7,8}</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., $\geq 9.0\%$) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥ 10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> • Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. • Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} $\geq 8.5\%$) makes it unlikely that another drug will be of sufficient benefit. • In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. • Increasing the number of drugs heightens the potential for side effects and drug-

Clinical Guideline	Recommendation(s)																																																																																																									
	<p>drug interactions which can negatively impact patient adherence.</p> <p>Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations</p> <table border="1"> <tr> <td data-bbox="505 296 691 342">Initial Drug Monotherapy</td> <td colspan="6" data-bbox="691 296 1408 342">Metformin</td> </tr> <tr> <td data-bbox="505 342 691 373">Efficacy (↓HbA_{1c})</td> <td colspan="6" data-bbox="691 342 1408 373">High</td> </tr> <tr> <td data-bbox="505 373 691 405">Hypoglycemia</td> <td colspan="6" data-bbox="691 373 1408 405">Low risk</td> </tr> <tr> <td data-bbox="505 405 691 436">Weight</td> <td colspan="6" data-bbox="691 405 1408 436">Neutral/loss</td> </tr> <tr> <td data-bbox="505 436 691 468">Side Effects</td> <td colspan="6" data-bbox="691 436 1408 468">Gastrointestinal/lactic acidosis</td> </tr> <tr> <td colspan="7" data-bbox="505 468 1408 510">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td> </tr> <tr> <td data-bbox="505 510 618 625">Two Drug Combinations</td> <td data-bbox="618 510 748 625">Metformin + sulfonyl-urea</td> <td data-bbox="748 510 878 625">Metformin + thiazolidinedione (TZD)</td> <td data-bbox="878 510 1008 625">Metformin + DPP-4 inhibitor</td> <td data-bbox="1008 510 1138 625">Metformin + SGLT2 inhibitor</td> <td data-bbox="1138 510 1268 625">Metformin + GLP-1 receptor agonist</td> <td data-bbox="1268 510 1408 625">Metformin + insulin (usually basal)</td> </tr> <tr> <td data-bbox="505 625 618 657">Efficacy (↓HbA_{1c})</td> <td data-bbox="618 625 748 657">High</td> <td data-bbox="748 625 878 657">High</td> <td data-bbox="878 625 1008 657">Inter-mediate</td> <td data-bbox="1008 625 1138 657">Inter-mediate</td> <td data-bbox="1138 625 1268 657">High</td> <td data-bbox="1268 625 1408 657">Highest</td> </tr> <tr> <td data-bbox="505 657 618 688">Hypoglycemia</td> <td data-bbox="618 657 748 688">Moderate risk</td> <td data-bbox="748 657 878 688">Low risk</td> <td data-bbox="878 657 1008 688">Low risk</td> <td data-bbox="1008 657 1138 688">Low risk</td> <td data-bbox="1138 657 1268 688">Low risk</td> <td data-bbox="1268 657 1408 688">High risk</td> </tr> <tr> <td data-bbox="505 688 618 720">Weight</td> <td data-bbox="618 688 748 720">Gain</td> <td data-bbox="748 688 878 720">Gain</td> <td data-bbox="878 688 1008 720">Neutral</td> <td data-bbox="1008 688 1138 720">Loss</td> <td data-bbox="1138 688 1268 720">Loss</td> <td data-bbox="1268 688 1408 720">Gain</td> </tr> <tr> <td data-bbox="505 720 618 877">Major Side Effects</td> <td data-bbox="618 720 748 877">Hypoglycemia</td> <td data-bbox="748 720 878 877">Edema, heart failure, bone fracture</td> <td data-bbox="878 720 1008 877">Rare</td> <td data-bbox="1008 720 1138 877">Genitourinary, dehydration</td> <td data-bbox="1138 720 1268 877">Gastrointestinal</td> <td data-bbox="1268 720 1408 877">Hypoglycemia</td> </tr> <tr> <td colspan="7" data-bbox="505 877 1408 930">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td> </tr> <tr> <td data-bbox="505 930 618 1077">Three Drug Combinations</td> <td data-bbox="618 930 748 1077">Metformin + sulfonyl-urea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin</td> <td data-bbox="748 930 878 1077">Metformin + TZD + Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin</td> <td data-bbox="878 930 1008 1077">Metformin + DPP-4 inhibitor + Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin</td> <td data-bbox="1008 930 1138 1077">Metformin + SGLT2 inhibitor + Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin</td> <td data-bbox="1138 930 1268 1077">Metformin + GLP-1 receptor agonist + Sulfonyl-urea, TZD, or insulin</td> <td data-bbox="1268 930 1408 1077">Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist</td> </tr> <tr> <td colspan="7" data-bbox="505 1297 1408 1371">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td> </tr> <tr> <td data-bbox="505 1371 691 1436">More Complex Insulin Strategies</td> <td colspan="6" data-bbox="691 1371 1408 1436">Combination injectable therapy</td> </tr> </table>	Initial Drug Monotherapy	Metformin						Efficacy (↓HbA _{1c})	High						Hypoglycemia	Low risk						Weight	Neutral/loss						Side Effects	Gastrointestinal/lactic acidosis						If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)							Two Drug Combinations	Metformin + sulfonyl-urea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)	Efficacy (↓HbA _{1c})	High	High	Inter-mediate	Inter-mediate	High	Highest	Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk	Weight	Gain	Gain	Neutral	Loss	Loss	Gain	Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)							Three Drug Combinations	Metformin + sulfonyl-urea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + TZD + Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + DPP-4 inhibitor + Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin	Metformin + SGLT2 inhibitor + Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin	Metformin + GLP-1 receptor agonist + Sulfonyl-urea, TZD, or insulin	Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist	If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents							More Complex Insulin Strategies	Combination injectable therapy					
Initial Drug Monotherapy	Metformin																																																																																																									
Efficacy (↓HbA _{1c})	High																																																																																																									
Hypoglycemia	Low risk																																																																																																									
Weight	Neutral/loss																																																																																																									
Side Effects	Gastrointestinal/lactic acidosis																																																																																																									
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)																																																																																																										
Two Drug Combinations	Metformin + sulfonyl-urea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)																																																																																																				
Efficacy (↓HbA _{1c})	High	High	Inter-mediate	Inter-mediate	High	Highest																																																																																																				
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk																																																																																																				
Weight	Gain	Gain	Neutral	Loss	Loss	Gain																																																																																																				
Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia																																																																																																				
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)																																																																																																										
Three Drug Combinations	Metformin + sulfonyl-urea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + TZD + Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + DPP-4 inhibitor + Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin	Metformin + SGLT2 inhibitor + Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin	Metformin + GLP-1 receptor agonist + Sulfonyl-urea, TZD, or insulin	Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist																																																																																																				
If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents																																																																																																										
More Complex Insulin Strategies	Combination injectable therapy																																																																																																									
<p>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)⁹</p>	<ul style="list-style-type: none"> • Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. • Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. • It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. 																																																																																																									
<p>American Association of Clinical Endocrinologists/ American College Of Endocrinology: Clinical Practice Guidelines for</p>	<p>Antihyperglycemic pharmacotherapy for type 2 diabetes</p> <ul style="list-style-type: none"> • The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement. • Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or 																																																																																																									

Clinical Guideline	Recommendation(s)
<p>Developing a Diabetes Mellitus Comprehensive Care Plan (2015)¹⁰</p>	<p>when a patient, whether drug naïve or not, has symptomatic hyperglycemia.</p> <ul style="list-style-type: none"> • Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. • Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. • When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. • The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. • When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists: Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm 2016 (2016)¹¹</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} \leq6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition

Clinical Guideline	Recommendation(s)
	<p>cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain.</p> <ul style="list-style-type: none"> The therapeutic regimen should be as simple as possible to optimize adherence. <p>Monotherapy</p> <ul style="list-style-type: none"> Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> GLP-1 receptor agonists. Sodium glucose cotransporter 2 (SGLT-2) inhibitors. DPP-4 inhibitors. . TZDs (use with caution). Alpha-glucosidase inhibitors. sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p>Combination therapy</p> <ul style="list-style-type: none"> Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: <ul style="list-style-type: none"> GLP-1 receptor agonists. SGLT-2 inhibitors. DPP-4 inhibitors. TZD. Basal insulin. Colesevelam. Bromocriptine quick release. Alpha-glucosidase inhibitors. Sulfonylureas and glinides. <p>Three-drug combination therapy</p> <ul style="list-style-type: none"> Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of reaching target with a third agent. Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. Continuation with noninsulin therapies while starting basal insulin is common

Clinical Guideline	Recommendation(s)
	<p>and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfoarea are used in conjunction with insulin.</p> <ul style="list-style-type: none"> • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Insulin therapy algorithm</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <p><u>Basal insulin</u></p> <ul style="list-style-type: none"> • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p><u>Basal-bolus insulin regimens</u></p> <ul style="list-style-type: none"> • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. <p><u>Basal insulin and incretin therapy regimens</u></p> <ul style="list-style-type: none"> • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and

Clinical Guideline	Recommendation(s)
	<p>postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.</p>
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last updated July 2016)¹²</p>	<p><u>Individualized care</u></p> <ul style="list-style-type: none"> • Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective. • Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p><u>HbA_{1c} targets</u></p> <ul style="list-style-type: none"> • Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. • For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. • In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> ○ reinforce advice about diet, lifestyle and adherence to drug treatment and ○ support the person to aim for an HbA_{1c} level of 7.0% and ○ intensify drug treatment. • Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> ○ who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy ○ for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job ○ for whom intensive management would not be appropriate, for example, people with significant comorbidities. • If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p><u>Drug treatment</u></p> <ul style="list-style-type: none"> • For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost • If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. • Initial drug treatment <ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults

Clinical Guideline	Recommendation(s)
	<p>with type 2 diabetes.</p> <ul style="list-style-type: none"> ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m²: <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p>First intensification of drug treatment</p> <ul style="list-style-type: none"> ● In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. ● In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. ● Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes. <p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> ● In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment. ● If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from

Clinical Guideline	Recommendation(s)
	<p>black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or</p> <ul style="list-style-type: none"> ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. <ul style="list-style-type: none"> ● Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in six months). ● In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment. ● In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. ● Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p><u>Insulin-based treatments</u></p> <ul style="list-style-type: none"> ● When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional. ● When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. ● Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation. ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: <ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes: <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. ● Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). ● Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. ● Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)¹³</p>	<ul style="list-style-type: none"> ● Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. ● A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. ● Recommend education and self-management, as appropriate. ● Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. ● Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes (2012)¹⁴</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> ● Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. ● Match the timing of medication (including insulin) and meals. ● Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Introduce physical activity gradually, based on the individual’s willingness and ability, and setting individualized and specific goals. • Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. • Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> • Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. • A lower HbA_{1c} target may be considered if it is easily and safely achieved. • A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> • Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. • Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. • First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. • Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. • Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering medications (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. <p><u>Insulin therapy</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)¹⁵</p>	<ul style="list-style-type: none"> • Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations ≥ 250 mg/dL. ○ Whose HbA_{1c} is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
<p>National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November 2016)¹⁶</p>	<p><u>Education and information for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. • Tailor the education programme to each child or young person with

Clinical Guideline	Recommendation(s)
	<p>type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as:</p> <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. <ul style="list-style-type: none"> ● Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. ● Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. ● Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. ● Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. ● Encourage children and young people with type 1 diabetes to wear or carry something that identifies them as having type 1 diabetes (e.g., a bracelet). ● Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. ● Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. ● Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations. ● Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p><u>Insulin therapy for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> ● While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. ● Take into account the personal and family circumstances of the child or young

Clinical Guideline	Recommendation(s)
	<p>person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen.</p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. • Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. • Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. • Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin infusion users. • Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. • Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin (0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%. • Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. • Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. • Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with type 1 diabetes a review of injection sites at each clinic visit. • Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. • If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily injections, continuous subcutaneous insulin infusion [CSII or insulin pump] therapy or once-, twice- or three-times daily mixed insulin injections). <p>Oral medicines for children and young people with type 1 diabetes</p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. <p><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. • Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. • Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. • Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain. <p><u>Education and information for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ HbA_{1c} monitoring and targets ○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control ○ the aims of metformin therapy and possible adverse effects ○ the complications of type 2 diabetes and how to prevent them. • Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every 2 years. • Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible

Clinical Guideline	Recommendation(s)
	<p>government disability benefits.</p> <ul style="list-style-type: none"> • Take particular care when communicating with and providing information to children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. <p><u>Dietary management for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. • Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. • At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. • Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications. • Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. • Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. • At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI. • Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. • Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy. <p><u>Metformin</u></p> <ul style="list-style-type: none"> • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management (Published 2015; last updated July 2016)¹⁷</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> • Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. • Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target. • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles ○ total glycated hemoglobin estimation (if abnormal hemoglobins). • Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. • Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking

Clinical Guideline	Recommendation(s)
	<p>into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia.</p> <ul style="list-style-type: none"> • Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p><u>Self-monitoring of blood glucose</u></p> <ul style="list-style-type: none"> • Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least four times a day, including before each meal and before bed. • Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). • Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia. • Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. • Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy) • Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking. <p><u>Continuous glucose monitoring</u></p> <ul style="list-style-type: none"> • Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. • Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause. ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level ≥9%) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in HbA_{1c} of 2.5% or more. • For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy.

Clinical Guideline	Recommendation(s)
	<p><u>Insulin regimens</u></p> <ul style="list-style-type: none"> • Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. • Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only). <p><u>Long-acting insulin</u></p> <ul style="list-style-type: none"> • Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. • Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul style="list-style-type: none"> ○ an existing insulin regimen being used by the person that is achieving their agreed targets ○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. • Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p><u>Rapid-acting insulin</u></p> <ul style="list-style-type: none"> • Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. • Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. • If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. <p><u>Mixed insulin</u></p> <ul style="list-style-type: none"> • Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. • Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p><u>Optimizing insulin therapy</u></p> <ul style="list-style-type: none"> • For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously optimized insulin regimen, the following should be considered: <ul style="list-style-type: none"> ○ injection technique ○ injection sites ○ self-monitoring skills ○ knowledge and self-management skills ○ nature of lifestyle ○ psychological and psychosocial difficulties ○ possible organic causes such as gastroparesis. • Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. <p><u>Adjuncts</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> • Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. • Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. • Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. • After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. • Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. • Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. • Check injection site condition at least annually and if new problems with blood glucose control occur.
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)¹⁸</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> • Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. • If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <p><u>Glycemic control goals</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p> <ul style="list-style-type: none"> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the meglitinides are noted in Table 3.

Table 3. FDA-Approved Indications for the Meglitinides¹⁻⁵

Indication	Single Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide and metformin
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✓	✓	
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have			✓

Indication	Single Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide and metformin
inadequate glycemic control on a meglitinide alone or metformin alone			

IV. Pharmacokinetics

The pharmacokinetic parameters of the meglitinides are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Meglitinides⁴

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Nateglinide	72 to 75	97 to 99	Liver, extensive (% not reported)	Renal (13 to 14), Feces (10)	1.25 to 2.90
Repaglinide	56	>98	Liver, complete (% not reported)	Renal (8), Feces (90)	1
Combination Products					
Repaglinide and metformin	56/50 to 60	>98/Negligible (% not reported)	Liver, complete (% not reported)/Liver, none (% not reported)	Renal (8), Feces (90)/Renal (90)	1.0/6.2

V. Drug Interactions

Major drug interactions with the meglitinides are listed in Table 5.

Table 5. Major Drug Interactions with the Meglitinides⁴

Generic Name(s)	Interaction	Mechanism
Metformin	Iodinated contrast materials, parenteral	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis.
Meglitinides	Fluoroquinolone antibiotics	Concurrent use of fluoroquinolones and antidiabetic agents may result in changes in blood glucose and increased risk of hypoglycemia or hyperglycemia. Monitor blood glucose levels when starting or stopping antibiotic therapy and adjust the repaglinide dose as needed.
Repaglinide	Gemfibrozil	Gemfibrozil may inhibit repaglinide metabolism (cytochrome P450 2C8 isoenzyme) causing elevated repaglinide plasma concentrations and increasing the risk of severe and protracted hypoglycemia. Avoid coadministration of repaglinide and gemfibrozil and reduce the dose of repaglinide when used together.
Repaglinide	Itraconazole	Concurrent use of itraconazole and repaglinide may result in increased plasma concentrations of repaglinide.
Repaglinide	Clopidogrel	Concurrent use of clopidogrel and repaglinide may result in increased repaglinide exposure.
Repaglinide	Teriflunomide	Concurrent use of repaglinide and teriflunomide may result in increased repaglinide exposure.
Repaglinide	Atazanavir	Concurrent use of atazanavir and repaglinide may result in increased repaglinide exposure or loss of glycemic control.
Repaglinide	Abiraterone	Concurrent use of abiraterone and repaglinide may result in increased repaglinide plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the meglitinides are listed in Table 6. The boxed warning for repaglinide/metformin is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Meglitinides¹⁻⁵

Adverse Events	Single Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide and metformin
Cardiovascular			
Arrhythmia	-	≤1	≤1
Chest pain	-	<2	<2
EEG abnormal	-	≤1	≤1
Hypertension	-	≤1	≤1
Myocardial infarction	-	≤1	≤1
Palpitations	-	≤1	≤1
Central Nervous System			
Dizziness	4	-	-
Headache	-	9 to 11	22
Dermatologic			
Pruritus	✓	-	-
Rash	✓	-	-
Urticaria	✓	-	-
Endocrine/Metabolic			
Hypoglycemia	2	16 to 31	33
Gastrointestinal			
Constipation	-	2 to 3	-
Diarrhea	3.2	4 to 5	19
Dyspepsia	-	2 to 4	-
Nausea	-	3 to 5	15
Vomiting	-	2 to 3	>5
Hepatic			
Hepatic dysfunction	-	✓	✓
Hepatitis	✓	✓	✓
Jaundice	✓	✓	✓
Laboratory Test Abnormalities			
Hemolytic anemia	-	✓	✓
Liver enzymes increased	✓	✓	✓
Thrombocytopenia	-	✓	✓
Uric acid increased	✓	-	-
Musculoskeletal			
Arthralgia	3	3 to 6	-
Back pain	4	5 to 6	-
Paresthesia	-	2 to 3	-
Respiratory			
Bronchitis	2.7	2 to 6	-
Coughing	2.4	-	-
Rhinitis	-	3 to 7	-
Sinusitis	-	3 to 6	-
Upper respiratory infection	10	10 to 16	11
Other			
Accidental trauma	2.9	-	-
Allergy	-	1 to 2	-
Alopecia	-	✓	✓
Anaphylactic reaction	-	✓	✓

Adverse Events	Single Entity Agents		Combination Products
	Nateglinide	Repaglinide	Repaglinide and metformin
Blurred vision	-	✓	✓
Flu symptoms	4	-	-
Pancreatitis	-	✓	✓
Stevens-Johnson Syndrome	-	✓	✓
Tooth disorder	-	2	-
Urinary tract infection	-	2 to 3	-
Weight gain	✓	-	-

✓ Percent not specified.

-Event not reported.

Table 7. Boxed Warning for Repaglinide/Metformin⁵

WARNING
Lactic acidosis: Lactic acidosis is a rare but serious complication that can occur because of metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic function impairment, renal function impairment, and acute congestive heart failure. The onset of lactic acidosis is often subtle and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, discontinue repaglinide/metformin and hospitalize the patient immediately.

VII. Dosing and Administration

The usual dosing regimens for the meglitinides are listed in Table 8.

Table 8. Usual Dosing Regimens for the Meglitinides¹⁻⁵

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Nateglinide	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 60 to 120 mg TID before meals; maintenance, 120 mg TID before meals	Safety and efficacy in children have not been established.	Tablet: 60 mg 120 mg
Repaglinide	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 0.5 to 2 mg with meals; maintenance, 0.5 to 4 mg with meals; maximum, 16 mg/day	Safety and efficacy in children have not been established.	Tablet: 0.5 mg 1 mg 2 mg
Combination Products			
Repaglinide and metformin	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone:</u> Tablet: initial, 1-500 mg BID to TID with meals, unless the patient is already taking higher coadministered doses of repaglinide and metformin; maximum, 4-1,000 mg/day	Safety and efficacy in children have not been established.	Tablet: 1-500 mg 2-500 mg

BID=twice daily, TID=three times daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the meglitinides are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Meglitinides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
<p>Rosenstock et al.¹⁹ (2004)</p> <p>Nateglinide 60 mg TID before each meal (titrated to a maximum of 360 mg daily)</p> <p>vs</p> <p>repaglinide 0.5 mg TID before each meal (titrated to a maximum of 16 mg daily)</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m², HbA_{1c} 7.0 to 12.0%, and drug naïve</p>	<p>N=150</p> <p>16 weeks</p>	<p>Primary: Final HbA_{1c} and changes in HbA_{1c} from baseline</p> <p>Secondary: Changes in FPG from baseline</p>	<p>Primary: Mean baseline HbA_{1c} values were similar in both groups (8.9%). The changes in HbA_{1c} for repaglinide from baseline were -1.57 vs -1.04% for nateglinide (P=0.002). Final HbA_{1c} values were lower in the repaglinide group vs the nateglinide group (7.3 vs 7.9%, respectively).</p> <p>At the end of the study, 54% of the repaglinide-treated patients had HbA_{1c} values ≤7.0% vs 42% of nateglinide-treated patients (P=0.18).</p> <p>Secondary: The final FPG was 154.0±40.2 mg/dL for repaglinide and 188.0±62.2 mg/dL for nateglinide. The mean change from baseline in FPG was greater with repaglinide compared to nateglinide (-57 vs -18 mg/dL; P<0.001).</p> <p>There were no major hypoglycemic episodes (requiring the assistance of another person) in either treatment group.</p> <p>Mean weight gains from baseline to the study end point were 1.8 kg for repaglinide and 0.7 kg for nateglinide (incremental mean imputation method calculation P=0.04 and P=0.034 by last observed carried forward method calculation).</p> <p>The most common adverse events (3 to 10% of patients in both treatment groups) were upper respiratory tract infection, sinusitis, constipation, arthralgia, headache, and vomiting. There were no notable differences in the pattern of adverse events for the treatment groups.</p>
<p>Li et al.²⁰ (2007)</p> <p>Nateglinide 90 mg TID before each</p>	<p>DB, DD, MC, RCT</p> <p>Chinese patients 35 to 65 years of age with type 2</p>	<p>N=223</p> <p>12 weeks</p>	<p>Primary: FPG, HbA_{1c}, TG, TC, BMI, HOMA-IR, β-cell function indexes, plasma</p>	<p>Primary: Compared to baseline, FPG; 30-, 60-, and 120-minute PPG; and HbA_{1c} all decreased significantly with both repaglinide and nateglinide treatment (P<0.05). Effects on FPG and PPG of the two agents were not significantly different (P>0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>meal vs repaglinide 1 mg TID before each meal</p>	<p>diabetes, on a stable diet and exercise for 4 weeks, with fasting blood glucose ≥ 7.8 mmol/L and/or 2-hour PPG ≥ 11.1 mmol/L at least twice in 2 weeks, without a history of antidiabetic agents other than metformin (on stable dosage for 4 weeks)</p>		<p>insulin, C-peptide, PPG using the incremental AUC (AUC_{0-120 min}) after a standard 800-kcal meal (55% carbohydrate, 25% fat and 20% protein)</p> <p>Secondary: Not reported</p>	<p>The HbA_{1c} levels at week 12 of the repaglinide group and the nateglinide group were not significantly different (6.27 vs 6.59%, respectively; P>0.05). However, an HbA_{1c} reduction at week 12 from baseline in the repaglinide group was significantly greater than an HbA_{1c} reduction in the nateglinide group (-1.21 vs -0.68%, respectively; P=0.0039).</p> <p>AUC of glucose significantly decreased in both repaglinide and nateglinide groups at week 12 to a similar extent (20.36±4.67 vs 20.54±4.83 mmol/L/h, respectively; P<0.0001 vs baseline; P>0.05 between the groups).</p> <p>AUC of insulin and C-peptide in both groups were increased at week 12 to a similar extent (P<0.05 vs baseline; P>0.05 between two groups).</p> <p>HOMA-IR in both groups were decreased significantly, and effects of repaglinide and nateglinide on insulin sensitivity were not different (2.44 vs 2.48, at week 12 respectively; P<0.05 vs baseline; P>0.05 between the groups).</p> <p>β-cell function indexes were increased in both groups, but the values were not significantly different between two groups after 12 weeks of treatment (P<0.05 vs baseline; P>0.05 between the groups).</p> <p>After the 12 weeks of treatment with repaglinide, TG level significantly decreased from baseline (no values reported; P<0.05). In both groups, TC level was decreased from baseline at week 12 (no values reported; P<0.05), and BMI was reduced slightly (P>0.05). Effects of both agents on TG, TC and BMI were not different (no values reported; P>0.05).</p> <p>Adverse events between the groups were reported to be similar (P>0.05). However, the rate of adverse reaction was reported to be 4.5% (hypoglycemic event, thrombocytopenia, elevation of liver enzymes) in the repaglinide group and 0.87% (thrombocytopenia) in the nateglinide group.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Hollander et al. ²¹ (2003) Nateglinide 120 mg TID before each meal vs glyburide 5 mg to 10 mg QD vs placebo	DB, MC, PC, RCT Patients 32 to 75 years of age with type 2 diabetes ≥3 months prior to entry into the trial on diet modification alone for ≥4 weeks before initial visit, mean HbA _{1c} 6.8 to 11.0%, and a BMI 20 to 35 kg/m ²	N=152 8 weeks	Primary: Change from week 0 to week eight during liquid meal challenges in FPG, fasting insulin, fasting C-peptide, and fasting proinsulin Secondary: Not reported	Primary: At week eight, FPG was reduced more with glyburide compared to nateglinide (-1.9 mmol/L; P<0.001). Nateglinide treatment did not have significant changes from baseline with fasting levels of C-peptide, insulin, or proinsulin. Glyburide treatment increased fasting C-peptide vs placebo and nateglinide (P<0.001), fasting insulin vs placebo (P<0.001) and nateglinide (P<0.05), and proinsulin vs placebo (P<0.001) and nateglinide (P<0.025). Reduction of mealtime glucose excursions from nateglinide was approximately twice that from glyburide (-4.94±0.74 vs -2.71±0.71 mmol/hr/L; P<0.03). The insulin secretion reflected by the C-peptide AUCs was approximately twice that in the glyburide group than in the nateglinide group (1.83±0.24 vs 0.95±0.23 nmol/hr/L, respectively; P=0.063 vs nateglinide). Secondary: Not reported
Wolffenbittel et al. ²² (1999) Repaglinide 0.5 to 4 mg TID before each meal vs glyburide 1.75 to 10.5 mg daily	DB, MC, PG, RCT Patients 40 to 75 years of age with type 2 diabetes who were being treated with oral blood glucose-lowering agents and/or diet, BMI 21 to 35 kg/m ² , and an HbA _{1c} >6.5% when treated with diet only and <12%	N=424 12 months	Primary: Change in HbA _{1c} and FPG from baseline to the final visit Secondary: Change in fasting insulin and lipid levels and four-point blood glucose levels (fasting, before lunch, before	Primary: Change in HbA _{1c} levels was not different between groups when compared to baseline. HbA _{1c} levels increased by 0.58% (95% CI, 0.41 to 0.76) in the repaglinide group and by 0.45% (95% CI, 0.22 to 0.69) in the glyburide group. In a subset of patients who were treated previously with diet only, HbA _{1c} decreased significantly more during glyburide treatment (-2.4%) vs repaglinide (-1%; P<0.05). The changes in HbA _{1c} in patients who were already being treated with oral agents were similar, 0.6% in the repaglinide group and 0.7% in the glyburide group. Changes in fasting plasma glucose from baseline showed a similar trend as the HbA _{1c} .

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	when treated with diet plus oral blood glucose-lowering agents		supper, and at bedtime) from baseline to the final visit	<p>Secondary: Mean fasting insulin levels decreased in the repaglinide group (-3 pmol/L) and increased in the glyburide group (+1 pmol/L). There was no treatment difference.</p> <p>Changes from baseline in four-point glucose levels were small for both treatment groups.</p> <p>Lipid levels (TC, HDL, and TG) did not change during the study.</p>
<p>Derosa et al.²³ (2003)</p> <p>Repaglinide 1 to 2.5 mg daily</p> <p>vs</p> <p>glimepiride 1 to 3 mg daily</p>	<p>DB, PC, RCT</p> <p>Patients with type 2 diabetes for ≥6 months, drug naïve, and HbA_{1c} >7.0% with diet and exercise</p>	<p>N=124</p> <p>12 months</p>	<p>Primary: Changes from baseline in HbA_{1c}, FPG, PPG, fasting plasma insulin, lipoprotein(a), plasminogen activator inhibitor-1, homocysteine, body weight, BMI, postprandial insulin, BP, TC, LDL-C, HDL-C, TG, apolipoprotein A-1, apolipoprotein B, and fibrinogen</p> <p>Secondary: Not reported</p>	<p>Primary: Changes in HbA_{1c} and FPG from baseline were significant for both treatments (P<0.01).</p> <p>Changes in PPG were significant for repaglinide vs baseline (P<0.01) and compared to glimepiride (P<0.05). Changes in PPG from baseline for the glimepiride group was significant (P<0.05).</p> <p>Change in fasting plasma insulin from baseline was significant for repaglinide (P<0.05).</p> <p>Changes in lipoprotein(a) from baseline were significant for repaglinide (P<0.05) and glimepiride (P<0.01).</p> <p>Changes in plasminogen activator inhibitor-1 from baseline were significant for both treatment groups (P<0.05).</p> <p>Changes in homocysteine were significant from baseline for repaglinide (P<0.05) and glimepiride (P<0.01). Changes in homocysteine were significant for glimepiride vs repaglinide (P<0.05).</p> <p>There were no significant changes during the study from baseline at six or 12 months in the following parameters for either treatment group: body weight, BMI, postprandial insulin, BP, TC, LDL-C, HDL-C, TG, apolipoprotein A-1, apolipoprotein B, and fibrinogen.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Cesur et al.²⁴ (2007)</p> <p>Repaglinide up to 4 mg QD</p> <p>vs</p> <p>glimepiride up to 8 mg QD</p> <p>vs</p> <p>insulin glargine up to 36 U QD</p>	<p>MC, OL, OS, PRO</p> <p>Patient 33 to 67 years of age with type 2 diabetes, HbA_{1c} 6.0 to 8.0% taking oral diabetes agents, who were willing to fast throughout Ramadan month</p>	<p>N=65</p> <p>Duration not specified</p>	<p>Primary: FBG, PPG, HbA_{1c}, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and post-Ramandan fasting</p> <p>Secondary: Not reported</p>	<p>Not reported</p> <p>Primary: In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan.</p> <p>In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan (P<0.05 and P<0.01, respectively). At post-Ramadan and one-month post-Ramadan, changes in PPG values in the fasting group were lower compared to the nonfasting group (P<0.01 for both time periods).</p> <p>There was no significant change in HbA_{1c} levels between the nonfasting and fasting groups.</p> <p>There was a significant increase in fructosamine levels in both fasting group and non-fasting group at one-month post-Ramadan (P<0.01 for both).</p> <p>BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group (P<0.05 between pre-Ramadan and post-Ramadan in nonfasting group).</p> <p>TC, LDL-C, and TG did not change throughout the study period but HDL-C levels significantly increased at post-Ramadan in the fasting group (P<0.01). In nonfasting group, LDL-C and TG levels significantly increased at post-Ramadan (P<0.05 for both).</p> <p>At least one hypoglycemia episode was reported in 12.2% of patients in the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Taki et al. ²⁵ (2005) Nateglinide	OS Patients with type 2 diabetes, drug naïve, with FPG ≤150 mg/dL and had started to take nateglinide alone	N=547 12 weeks	Primary: HbA _{1c} , PPG, FPG, hypoglycemia Secondary: Not reported	Primary: In the nateglinide group, a reduction in HbA _{1c} was 0.82%, PPG was 59.4 to 158.0 mg/dL, and FPG was 11.7 to 122.4 mg/dL. Hypoglycemia was the most prevalent adverse event (2.1%). A total of nine of 11 episodes required no therapeutic intervention. Severe hypoglycemia was recognized in one case of diabetes complicated by serious renal dysfunction, for which nateglinide has been contraindicated in Japan. No patient experienced symptoms of nocturnal or prolonged hypoglycemia. Secondary: Not reported
Taki et al. ²⁶ (2006) Nateglinide	OS Japanese patients with type 2 diabetes	N=1,014 15 months	Primary: PPG, FPG, HbA _{1c} , BMI Secondary: Not reported	Primary: In patients receiving nateglinide, there were reductions in PPG of -9.3 mg/dL (from 155.1±40.0 to 145.0±35.1 mg/dL) and HbA _{1c} of 0.68% (from 7.51±1.36 to 6.83±1.09%). In patients previously treated with sulfonylurea, a decrease in HbA _{1c} was not observed. No change in BMI was noted after 15 months of nateglinide treatment. Secondary: Not reported
Schwarz et al. ²⁷ (2008) Nateglinide 120 mg TID before meals vs placebo	DB, MC, PC, PG, RCT Patients 65 to 90 years of age with type 2 diabetes for ≥4 weeks, oral antidiabetic agents, with FPG ≤240 mg/dL, BMI 22 to 40 mg/m ² , HbA _{1c} 7.0 to 9.5%, without	N=54 12 weeks	Primary: Change in baseline HbA _{1c} Secondary: FPG, PPG, proportion of patients achieved a target HbA _{1c} <7.0 or ≤6.5%, adverse events	Primary: Plasma HbA _{1c} decreased from 7.6±0.1 to 6.9±0.1% in patients receiving nateglinide (mean change, -0.7±0.1%; P<0.001) compared to a reduction of 7.7±0.2 to 7.5±0.1% in patients receiving placebo (change, -0.2±0.2%; P=0.206). A significant difference between the two groups in HbA _{1c} change was reported (-0.5%; 95% CI, -1.0 to -0.2; P=0.004). Secondary: After 12 weeks of treatment, FPG decreased significantly from 164±6 to 141±7 mg/dL in patients receiving nateglinide (change, -23±7 mg/dL; P=0.003) compared to a reduction of 153±8 to 159±7 mg/dL in patients receiving placebo (change, 2±5 mg/dL; P=0.728). A significant difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>history of type 1 diabetes or secondary diabetes, significant symptomatic complications of diabetes, severe cardiac dysfunction, significant cardiovascular events within 6 months prior to randomization, and severe liver disease</p>			<p>between the two groups in FPG change was reported (-25 mg/dL; 95% CI, -40 to -3; P=0.022).</p> <p>Two-hour PPG decreased from 184±11 to 153±8 mg/dL in patients receiving nateglinide (change, -29±11 mg/dL; P=0.019) compared to a reduction of 192±14 to 188±15 mg/dL in patients receiving placebo (change, -7±17 mg/dL; P=0.687). A difference between two groups in Two-hour PPG change was significant (-36 mg/dL; 95% CI, -74 to -8; P=0.018).</p> <p>Sixty percent of patients in the nateglinide group achieved a target HbA_{1c} of <7.0% compared to 21% of patients in the placebo group (P=0.004).</p> <p>Significantly higher number of patients receiving nateglinide achieved a target HbA_{1c} ≤6.5% compared to placebo-treated patients (8/30 vs 1/24, respectively; P=0.028).</p> <p>Similar adverse-event profiles were reported between the two groups (15 patients in each group reported one or more adverse events). No serious adverse events, hypoglycemic events or deaths were reported.</p>
<p>Zhou et al.²⁸ (2013)</p> <p>Acarbose 50 mg TID</p> <p>nateglinide 120 mg TID</p>	<p>AC, ML, OL, PG, RCT</p> <p>Patients 18 to 75 years who were antihyperglycemic agent-naïve with type 2 diabetes (HbA_{1c} 6.5 to 9.0%)</p>	<p>N=103</p> <p>2 weeks</p>	<p>Primary: Incremental area under the curve of postprandial blood glucose (AUC_{pp}) during continuous glucose monitoring (CGM)</p> <p>Secondary: Additional CGM measures, serum glycosylated albumin, safety</p>	<p>Primary: Both treatment groups showed a significant decrease in the AUC_{pp} of treatment (vs baseline, P<0.001), but the decrease achieved by the two therapies was not significantly different (nateglinide vs acarbose, P=0.691).</p> <p>Secondary: No significant differences between treatment groups occurred for secondary efficacy outcomes, except for therapy-mediated effects on insulin levels. The insulin concentrations in the nateglinide group increased at 30 minutes (P<0.0001) and at 120 minutes (P=0.0012), with statistical differences between pretreatment and posttreatment. In contrast, compared with baseline, the insulin concentrations at the end point in the acarbose group decreased at 30 minutes and at 120 minutes with statistical differences between pretreatment and post-treatment (both P<0.0001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Chisalita et al.²⁹ (2009)</p> <p>Repaglinide 4 mg TID before meals for 10 weeks</p> <p>vs</p> <p>insulin aspart 13 to 46 units/day (4 to 20 units at breakfast, 5 to 15 units at lunch and 4 to 15 units at dinner) for 10 weeks</p>	<p>XO</p> <p>Patients ≥60 years of age with type 2 diabetes</p>	<p>N=5</p> <p>20 weeks</p>	<p>Primary: HbA_{1c}, blood glucose, C-peptide, free human insulin, free total (human and analogue) insulin, proinsulin, islet amyloid polypeptide, growth hormone binding protein, and plasma lipoprotein concentrations were measured</p> <p>Secondary: Not reported</p>	<p>Both treatments were well-tolerated.</p> <p>Primary: The HbA_{1c} was 6.1% at the end of repaglinide therapy and 5.9% at the end of insulin aspart therapy (P value not significant).</p> <p>C-peptide concentrations were significantly higher during repaglinide treatment compared to insulin aspart treatment (AUC 2,453 vs 1,153; P=0.02).</p> <p>Free human insulin levels were significantly higher on repaglinide than on insulin aspart therapy (AUC: 215 vs 128; P<0.05).</p> <p>Proinsulin levels were higher when measured during repaglinide treatment than during treatment with insulin aspart.</p> <p>Islet amyloid polypeptide levels tended to be higher during repaglinide compared to insulin aspart treatment (P value not significant).</p> <p>Fasting plasma insulin like growth factor-I concentration was 220 ng/mL during treatment with insulin aspart and 226 ng/mL during treatment with repaglinide (P value not significant).</p> <p>Compared to fasting levels, the insulin like growth factor binding protein-1 levels were lower during repaglinide (P<0.05), but not during insulin aspart treatment (P value not significant).</p> <p>Repaglinide treatment increased plasma growth hormone binding protein concentration compared with insulin aspart (1,094 vs 942 pmol/L; P=0.02).</p> <p>Repaglinide treatment resulted in higher postprandial plasma TC, TG and apolipoprotein B concentrations compared with insulin aspart. There was no significant difference in LDL-C or HDL-C</p> <p>Secondary: Not reported</p>
<p>Lund et al.³⁰</p>	<p>DD, XO</p>	<p>N=96</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Repaglinide 2 mg TID for 4 months vs metformin 1,000 mg BID for 4 months	Non-obese (BMI ≤ 27 kg/m ²), insulin-naïve patients with type 2 diabetes mellitus	8 months with 1 month washout	Cardiovascular disease biomarkers and metabolic regulation Secondary: Not reported	Levels of tumor necrosis factor-alpha, plasminogen activator inhibitor-1 antigen, tissue-type plasminogen activator antigen, von Willebrand factor, soluble intercellular adhesion molecule-1 and soluble E-selectin were significantly lower during metformin treatment compared with repaglinide treatments. Amadori albumin and heart rate were higher during metformin compared with repaglinide. Both treatment groups experienced similar levels of interleukin-6, fibrinogen, soluble vascular cell adhesion molecule-1, asymmetric dimethylarginine and advanced glycation end products as well as glycemic levels and 24 hour BP. Secondary: Not reported
Lund et al. ³¹ (2008) Repaglinide 2 mg TID for 4 months vs metformin 1,000 mg BID for 4 months	DD, XO Non-obese (BMI ≤ 27 kg/m ²), insulin-naïve patients with type 2 diabetes mellitus	N=192 8 months with 1 month washout	Primary: Postprandial metabolism with blood sampling 0 to six hours postprandially Secondary: Not reported	Primary: Both treatment groups equally changed fasting levels and total AUC for plasma glucose, TG and FFA. The metformin treatment group obtained lower fasting levels and AUC of TC, LDL-C, and non-HDL-C and serum insulin compared with repaglinide. After adjusting for fasting levels, AUC differences still remained significant. Secondary: Not reported
Fang et al. ³² (2014) Repaglinide vs metformin	OL, PG, RCT Chinese drug-naïve patients aged 20 to 90 years with newly diagnosed type 2 diabetes mellitus with a BMI of 18.5 to 30 kg/m ² and	N=60 15 weeks	Primary: Change in HbA _{1c} from baseline Secondary: Changes in glycemic variability, insulin sensitivity, β -cell	Primary: At week 15, mean changes in HbA _{1c} from baseline were $-1.8 \pm 1.5\%$ in the repaglinide group ($P < 0.01$) and $-1.6 \pm 1.5\%$ in the metformin group ($P < 0.01$). No significant difference was found with regard to change in HbA _{1c} level between the two groups ($P = 0.739$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	with an HbA _{1c} <10.0%		function	Secondary: No significant differences in secondary outcomes were found between the groups.
<p>Bolen et al.³³ (2007)</p> <p>Meglitinides</p> <p>vs</p> <p>biguanides</p> <p>vs</p> <p>TZDs</p> <p>vs</p> <p>α-glucosidase inhibitors</p> <p>vs</p> <p>second-generation sulfonylureas</p>	<p>MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs)</p> <p>Patients with type 2 diabetes</p>	<p>N=136 (articles on intermediate outcomes)</p> <p>N=167 (articles on adverse events)</p> <p>N=68 (articles on micro-vascular outcomes and mortality)</p> <p>Duration varied</p>	<p>Primary: Intermediate outcomes: HbA_{1c}, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes</p> <p>Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events</p>	<p>Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA_{1c} level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.</p> <p>TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C.</p> <p>TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP.</p> <p>Most agents except metformin increased body weight by 1 to 5 kg.</p> <p>In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05).</p> <p>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).</p> <p>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).</p> <p>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.</p> <p>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.</p> <p>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.</p>
<p>Monami et al.³⁴ (2008)</p> <p>Metformin</p> <p>vs</p> <p>sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists</p>	<p>MA</p> <p>Patients with type 2 diabetes mellitus</p>	<p>N=7,890 (27 RCT)</p> <p>Variable duration</p>	<p>Primary: Reduction in HbA_{1c} at 16 to 36 months</p> <p>Secondary: Not reported</p>	<p>Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.</p> <p>In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.</p> <p>Secondary: Not reported</p>
<p>Saenz et al.³⁵ (2005)</p> <p>Metformin monotherapy</p> <p>vs</p>	<p>MA (29 RCTs)</p> <p>Adult patients with type 2 diabetes</p>	<p>N=5,259</p> <p>≥3 months</p>	<p>Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal</p>	<p>Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03).</p> <p>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo, sulfonylureas, TZDs, meglitinides, α -glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin			MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypoglycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA _{1c} , FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, microalbuminuria, glomerular filtration rate, renal plasma flow	mortality (P=0.01), and MI (P=0.02). Secondary: Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA _{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.
Gangji et al. ³⁶ (2007)	MA (21 trials) Patients with type 2	N=not reported	Primary: Hypoglycemia, glycemic control,	Primary: Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Glyburide</p> <p>vs</p> <p>sulfonylureas, meglitinides, insulin</p>	<p>diabetes</p>	<p>Duration varied</p>	<p>cardiovascular events, body weight, death</p> <p>Secondary: Not reported</p>	<p>95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49).</p> <p>Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues.</p> <p>Secondary: Not reported</p>
<p>Richter et al.³⁷ (2007)</p> <p>Rosiglitazone monotherapy (10 trials) vs glyburide (2 trials), metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial)</p> <p>or</p> <p>rosiglitazone combination therapy vs a similar combination with another compound (8 trials)</p> <p>Some studies had more than 1 treatment arm.</p>	<p>MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG</p> <p>Adults with type 2 diabetes, trial duration of at least 24 weeks</p>	<p>18 trials</p> <p>N=3,888 randomized to rosiglitazone treatment (total N not reported)</p> <p>24 weeks to 4 years (median 26 weeks)</p>	<p>Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects</p> <p>Secondary: Health-related quality of life, metabolic control (HbA_{1c})</p>	<p>Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference).</p> <p>The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference).</p> <p>The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in body mass index up to 1.5 kg/m². Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01).</p> <p>Secondary: No study investigated health-related quality of life.</p> <p>Active glucose-lowering compounds like metformin, glibenclamide* or glimepiride resulted in similar reductions of HbA_{1c} compared to rosiglitazone treatment.</p>
<p>Richter et al.³⁸ (2006)</p> <p>Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials)</p> <p>or</p> <p>pioglitazone combination</p>	<p>MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG</p> <p>Adults with type 2 diabetes, trial duration of at least 24 weeks</p>	<p>22 trials</p> <p>N=6,200 randomized to pioglitazone treatment (total N not reported)</p> <p>24 weeks to 34.5 months</p>	<p>Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects</p> <p>Secondary: Health-related quality of life, HbA_{1c}</p>	<p>Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095).</p> <p>Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).</p> <p>The percentage of overall and serious adverse events was comparable</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone)</p> <p>Some studies had more than 1 treatment arm.</p>				<p>between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in body mass index up to 1.5 kg/m². Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled.</p> <p>Secondary: No study investigated health-related quality of life.</p> <p>Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (P values not reported).</p>
<p>Kheirbek et al.³⁹ (2013)</p> <p>Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors)</p>	<p>OS, RETRO</p> <p>Veterans with diabetes cared for at a Veterans Administration Capital area medical center</p>	<p>N=17,773</p> <p>Variable duration</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Not reported</p>	<p>Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
*Defined as any use of the medication independent of dose or days of use				
Type 2 Diabetes – Combination Therapy				
<p>Raskin et al.⁴⁰ (2003)</p> <p>Nateglinide 120 mg TID before meals and metformin 1,000 mg BID</p> <p>vs</p> <p>repaglinide 1 to 4 mg TID before meals and metformin 1,000 mg BID</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m², HbA_{1c} 7.0 to 12.0% on previous monotherapy with a sulfonylurea, metformin, or low dose glyburide plus metformin</p>	<p>N=192</p> <p>16 weeks</p>	<p>Primary: Final HbA_{1c} values and changes in HbA_{1c} from baseline</p> <p>Secondary: Changes in FPG and assessment of glucose area under the time concentration curves from 0 to 240 minutes (AUC_{0-240 min}), insulin AUC_{0-240 min}, and glucagon AUC_{0-240 min} after a liquid test meal at baseline and at study end point</p>	<p>Primary: Mean HbA_{1c} changes from baseline were significantly greater in the repaglinide group compared to the nateglinide group (-1.28 vs -0.67%; P<0.001).</p> <p>The final HbA_{1c} at 16 weeks was 7.1±1.1% for the repaglinide group and 7.5±1.4% for the nateglinide group.</p> <p>The percent of patients who achieved final HbA_{1c} values ≤7.0% was 59% for the repaglinide group and 47% for the nateglinide group (P value not reported).</p> <p>Secondary: FPG values were significantly different between the two treatment groups with one week of therapy. Mean changes in FPG values from baseline were significantly greater for the repaglinide group (-39 vs -21 mg/dL for nateglinide group; P=0.002). The final FPG at 16 weeks was 150.0±45.1 mg/dL for the repaglinide group and 170±52 mg/dL for the nateglinide group. At the end of the 16 week maintenance study, 48% of the repaglinide group had reductions of FPG values >40 mg/dL and 26% of the nateglinide group had a response of this magnitude.</p> <p>Mean end point reductions in PPG levels from baseline were not significantly different between the groups (glucose AUC_{0-240 min}). The treatments were also similar for changes in insulin AUC_{0-240 min} and glucagon AUC_{0-240 min} during the study (P values not reported).</p> <p>There were no patients in either group who experienced major hypoglycemic episodes (requiring the assistance of another person).</p> <p>The most frequent adverse event in both groups was upper respiratory</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				infection (12 vs 21%). Adverse events that occurred from 3 to 8% included nausea, viral infection, accidental injury, sinusitis, diarrhea, and headache. The repaglinide group had 5% incidence of chest pain and arthralgia, as compared to 1% for each in the nateglinide groups. Mean changes from baseline in weight were small for both groups, 0.6 kg gain for repaglinide compared to 0.5 kg loss with nateglinide.
<p>Horton et al.⁴¹ (2000)</p> <p>Nateglinide 120 mg TID before each meal and metformin 500 mg TID immediately after the start of each meal</p> <p>vs</p> <p>nateglinide 120 mg TID before each meal</p> <p>vs</p> <p>metformin 500 mg TID immediately after the start of each meal</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, PRO, RCT</p> <p>Patients ≥ 30 years of age with type 2 diabetes for ≥ 3 months with a BMI 20 to 35 kg/m², and all patients needed to have been treated with diet alone with an HbA_{1c} 6.8 to 11.0% and FPG level ≤ 15 mmol/L</p>	<p>N=701</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c}, FPG, glucose AUC after Sustacal challenge from baseline</p> <p>Secondary: Not reported</p>	<p>Primary: Adjusted mean change from baseline in HbA_{1c}, FPG, and glucose AUC after Sustacal challenge were significantly reduced from baseline (P≤ 0.0001) in patients receiving active treatment.</p> <p>HbA_{1c}, FPG, and glucose AUC were all significantly reduced compared to placebo (P≤ 0.001), except from glucose AUC with metformin monotherapy.</p> <p>The decrease in HbA_{1c} was greater for metformin compared to nateglinide, the between group difference was small (0.3% difference; P≤ 0.01).</p> <p>The decrease in FPG was greater with the metformin group compared to the nateglinide group, the between group difference was 0.9 mmol/L (P≤ 0.001).</p> <p>The combination of nateglinide plus metformin was additive (HbA_{1c}, -1.4% and FPG, -2.4 mmol/L; P≤ 0.01 vs either monotherapy).</p> <p>After a Sustacal challenge, there was a greater reduction in mealtime glucose with nateglinide compared to metformin or placebo (AUC_{0-130 min}, -2.1, -1.1, and 0.6 mmol/hr/L, respectively; P≤ 0.0001). A greater reduction was seen with nateglinide plus metformin (AUC_{0-130 min}, -2.5 mmol/hr/L; P≤ 0.0001 vs metformin and placebo).</p> <p>Secondary: Not reported</p>
<p>Marre et al.⁴² (2002)</p> <p>Nateglinide 60 to</p>	<p>DB, MC, PG, RCT</p> <p>Patients ≥ 30 years of age with type 2</p>	<p>N=467</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p>	<p>Primary: Mean HbA_{1c} was reduced significantly from baseline when compared to the placebo group for the nateglinide 60 mg group (-0.36%; 95% CI, -0.59 to -0.13; P=0.003) and for the nateglinide 120 mg group (-0.51%; 95% CI,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>120 mg TID before meals and metformin 1,000 mg BID</p> <p>vs</p> <p>metformin 1,000 mg BID and placebo</p>	<p>diabetes for ≥ 6 months with HbA_{1c} 6.8 to 11.0%, BMI 20 to 35 kg/m², and were treated with metformin for a minimum of 3 months and stabilized at a dose of $\geq 1,500$ mg/day for ≥ 4 weeks prior to study entry</p>		<p>Secondary: Change in FPG, body weight, and lipid profile (TC, fasting TGs, LDL-C, HDL-C)</p>	<p>-0.82 to -0.36; P<0.001) at end point.</p> <p>Dose-dependent reduction in HbA_{1c} was seen with nateglinide irrespective of baseline parameters, with larger mean reductions seen with nateglinide 120 mg. There was little or no change in HbA_{1c} at end point in the placebo group.</p> <p>Secondary: There were modest changes from baseline in FBG in the nateglinide groups and an increase was seen in the placebo group, the difference compared to baseline was significant in both the nateglinide 60 and 120 mg groups (P=0.044 and P=0.003, respectively).</p> <p>There were no notable changes in body weight at end point in the patients that received placebo (0.1 kg) or nateglinide 60 mg (0.4 kg). There was a significant increase (P<0.001) in mean weight of 0.9 kg in the nateglinide 120 mg group as compared to baseline.</p> <p>Fasting TGs were significantly reduced in the nateglinide 120 mg group as compared to the placebo group at end point (P=0.042). The mean changes in TC, LDL-C, and HDL-C remained almost unchanged throughout the study.</p>
<p>Gerich et al.⁴³ (2003)</p> <p>Nateglinide 120 mg TID before meals and metformin 500 to 2,000 mg daily</p> <p>vs</p> <p>glyburide 1.25 to 10 mg daily and metformin 500 to 2,000 mg daily</p>	<p>DB, MC, RCT (PRESERVE-β Study)</p> <p>Men and women aged 18 to 77 years with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤ 15 mmol/L, BMI of 22 to 45 kg/m² and inadequately controlled on diet and exercise</p>	<p>N=428</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline (average of weeks -2 and 0) to week 104</p> <p>Secondary: Change from baseline to week 104 in FPG, and body weight</p>	<p>Primary: Both treatments maintained similar reductions in HbA_{1c}. The mean change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (-1.2 \pm 0.1%) was similar (P=0.1730) to that in the glyburide plus metformin group (-1.5 \pm 0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.0001) after one and two years of treatment and there was no significant difference between the groups.</p> <p>Secondary: Mean change in FPG was -1.6\pm0.2 mmol/L in patients in the nateglinide plus metformin group (P<0.0001 vs baseline) and -2.4\pm0.2 mmol/L in patients in the glyburide plus metformin group (P<0.0001 vs baseline; P=0.0078 vs nateglinide plus metformin).</p> <p>Body weight decreased in the nateglinide plus metformin group (-0.4</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>kg±0.4 kg) and increased in the glyburide plus metformin group (0.8 kg±0.5 kg). The change from baseline was significant for the glyburide plus metformin group (P=0.0011) only (P=0.8413 for the nateglinide plus metformin group). The difference between groups was statistically significant (P=0.0115).</p>
<p>Schwarz et al.⁴⁴ (2008)</p> <p>Nateglinide 120 mg TID before meals and metformin 2,000 mg QD</p> <p>vs</p> <p>glyburide 10 mg QD and metformin 2,000 mg QD</p>	<p>AC, DB, MC, RCT (PRESERVE-β Study – subgroup analysis)</p> <p>Men and women ≥65 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤15 mmol/L, BMI 22 to 45 kg/m²</p>	<p>N=69</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Change from baseline to week 104 in FPG, two-hour PPG using the incremental AUC (AUC_{0-120 min}) of glucose during oral glucose tolerance tests, the proportion of patients achieving a target HbA_{1c} <7.0 or ≤6.5%, adverse events</p>	<p>Primary: Similar reductions in HbA_{1c} were seen with both treatments. The average change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (−1.2±0.2%) was similar (P=0.310) to that in the glyburide plus metformin group (−1.2±0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.001) after two years of treatment and there was no significant difference between the groups.</p> <p>Secondary: Mean change in FPG was −26±6 mg/dL in patients receiving nateglinide plus metformin (P<0.001 vs baseline) and −36±6 mg/dL in patients receiving glyburide plus metformin (P<0.001 vs baseline) (P=0.234 between the groups).</p> <p>A non-significant reduction in two-hour PPG from baseline was reported in both the nateglinide plus metformin and glyburide plus metformin groups (−15±7 mg/dL; P=0.071 and −8±8 mg/dL; P=0.385, respectively).</p> <p>The proportion of patients who achieved a target HbA_{1c} <7.0% in the nateglinide plus metformin group was not significantly different compared to the glyburide plus metformin group (70 vs 65%, respectively; P=0.736).</p> <p>Similar proportions of patients in the nateglinide plus metformin group and the glyburide plus metformin group maintained a target HbA_{1c} ≤6.5% (40 and 60%, respectively; P=0.206).</p> <p>Approximately 94% of patients in the nateglinide plus metformin group and 88% of patients in the glyburide plus metformin group reported one or more adverse events. One mild hypoglycemic event occurred with nateglinide plus metformin treatment vs eight mild-to-severe hypoglycemic events with glyburide plus metformin treatment (P<0.023).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Fonseca et al.⁴⁵ (2003)</p> <p>Nateglinide 120 mg before each meal and rosiglitazone 8 mg QD</p> <p>vs</p> <p>rosiglitazone 8 mg QD and placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥21 years of age with type 2 diabetes for ≥6 months previously and treated with rosiglitazone 8 mg/day, diet, and exercise for ≥3 months, had a BMI 22 to 40 kg/m², FPG 6.1 to 13.3 mmol/L, and HbA_{1c} 7.0 to 11.0%</p>	<p>N=402</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, two-hour postprandial insulin, TC, LDL-C, HDL-C, TG, body weight, four-hour AUC for glucose, insulin during meal challenges</p>	<p>Primary: HbA_{1c} did not change significantly from baseline in the placebo group, but did change significantly in the nateglinide group. The change from baseline to end point was $-0.8 \pm 0.1\%$ ($P < 0.0001$ vs baseline or placebo).</p> <p>Secondary: Change in FPG decreased significantly from a baseline of 9.8 to 9.0 mmol/L in the nateglinide group ($P < 0.001$). FPG did not change significantly from the baseline (10 mmol/L) in patients receiving placebo.</p> <p>Two-hour postprandial insulin in the nateglinide group decreased from 14.0 to 11.4 mmol/L ($P < 0.0001$). The group receiving placebo had an increase in two-hour postprandial insulin from 14.4 to 14.8 mmol/L ($P < 0.0001$ vs nateglinide).</p> <p>Total and incremental glucose AUC_{S(0-4 hours)} were significantly reduced in the nateglinide group (-8.6 ± 0.8 and -6.2 ± 0.5 mmol/L/hr, respectively; $P < 0.0001$ vs baseline or placebo for both total and incremental AUCs). This represents a 16% reduction in the total and a 49% reduction in the incremental glucose AUC.</p> <p>Total and incremental insulin AUC_{S(0-4 hour)} were increased in the nateglinide group (425 and 395 pmol/L/hr, respectively; $P < 0.0001$ vs baseline or placebo plus for both total and incremental AUCs). This represents a 46% increase in the total and 69% increase in the incremental insulin AUC.</p> <p>There were no significant changes in TC, LDL-C, or TG in either group. There was a small, but significant increase from baseline in HDL-C observed in patients receiving nateglinide ($P < 0.025$) and in patients receiving placebo ($P < 0.005$).</p> <p>Body weight increased in both groups. The mean change from baseline in patients receiving nateglinide (3.1 ± 0.3 kg) was significantly greater compared to patients receiving placebo (1.1 ± 0.3 kg; $P < 0.0001$).</p> <p>Meal challenges were performed at week 0 and at end point. The glucose</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Moses et al.⁴⁶ (1999)</p> <p>Repaglinide 0.5 to 4 mg TID before each meal and metformin 1,000 to 3,000 mg daily</p> <p>vs</p> <p>repaglinide 0.5 to 4 mg TID before each meal</p> <p>vs</p> <p>metformin 1,000 to 3,000 mg daily</p>	<p>DB, MC, PG, RCT</p> <p>Patients 40 to 75 years of age with type 2 diabetes treated with metformin alone (1 to 3 g/day) for >6 months and had not achieved optimal glycemic control (HbA_{1c} >7.0%) and BMI ≥21 kg/m²</p>	<p>N=83</p> <p>3 months</p>	<p>Primary: Change in baseline HbA_{1c} and FPG</p> <p>Secondary: Change in fasting insulin, C-peptide levels, fasting TG, TC, HDL-C, LDL-C, free fatty acids, body weight</p>	<p>and insulin profiles were similar in the two groups at baseline, and PPG and insulin concentrations were unchanged at end point relative to baseline in patients receiving placebo.</p> <p>Primary: Patients in the metformin plus repaglinide group had a significant decrease in HbA_{1c} from 8.3 to 6.9% (P=0.0016) and FPG from 10.2 to 8.0 mmol/L (P=0.0003) compared to baseline. There were no significant changes in HbA_{1c} or FPG for patients receiving metformin alone and repaglinide alone. The HbA_{1c} and FPG changes from baseline for metformin plus repaglinide vs metformin alone and metformin plus repaglinide vs repaglinide were significant (P<0.05 for all).</p> <p>Secondary: Fasting insulin and C-peptide levels increased significantly from baseline in both groups receiving repaglinide (P<0.05 for both).</p> <p>Lipid levels (TC, HDL-C, LDL-C, TG, FFA) did not change significantly from baseline in the metformin plus repaglinide group. No significant differences were found between the metformin plus repaglinide group and the monotherapy groups.</p> <p>In both groups receiving repaglinide there was an increase in body weight which was significant compared to baseline (P<0.05 for both).</p>
<p>Raskin et al.⁴⁷ (2004)</p> <p>Repaglinide 0.5 to 4 mg TID before meals and rosiglitazone 2 to 4 mg BID</p> <p>vs</p> <p>repaglinide 0.5 to 4 mg TID before meals</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes for ≥12 months with an HbA_{1c} >7.0 to ≤12.0% during previous monotherapy with sulfonylurea or metformin for ≥3 months with a BMI ≤45 kg/m²</p>	<p>N=252</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG</p>	<p>Primary: Mean change in HbA_{1c} from baseline with repaglinide was -0.17% and -0.56% with rosiglitazone. The mean change in HbA_{1c} from baseline with combination therapy was -1.43 (P≤0.001 vs either monotherapy). The reduction in HbA_{1c} from baseline was greater with combination therapy compared to the sum of the responses for monotherapy (P<0.01).</p> <p>Secondary: Mean FPG change from baseline with repaglinide was -3 mmol/L and -3.7 mmol/L with rosiglitazone. Mean FPG change from baseline with combination therapy was -5.2 mmol/L (P≤0.001 vs either monotherapy).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rosiglitazone 2 to 4 mg BID				
Ozbek et al. ⁴⁸ (2006) Repaglinide 4.5 mg QD vs placebo All patients were also receiving insulin.	RCT Patients with type 2 diabetes who had been initially treated with oral antidiabetic agents without a satisfactory response (HbA _{1c} <7.0%), hospitalized in a single center for glycemic control with intensive insulin therapy involving multiple daily subcutaneous injections	N=50 3 months	Primary: Exogenous insulin requirements, HbA _{1c} , hypoglycemia Secondary: Not reported	Primary: A significant reduction in daily total exogenous insulin requirements was seen in the repaglinide group. The daily total insulin requirements were 57.4±14.8 and 28.8±13.8 units before and after the three month study period, respectively (P<0.01). Serum HbA _{1c} levels were 7.3±0.3 and 6.4±0.3% before and after the three month period in the repaglinide group (P<0.01). None of the patients experienced symptomatic hypoglycemia episode. Secondary: Not reported
Civera et al. ⁴⁹ (2008) Repaglinide 2mg TID before meals, metformin 850mg BID, and NPH insulin before dinner vs metformin 850mg	OL, PG Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs	N=37 24 weeks	Primary: HbA _{1c} , hypoglycemia, body weight Secondary: Not reported	Primary: The HbA _{1c} was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; P=0.02) and the NPH insulin group (8.4%; P=0.02). The absolute reduction in HbA _{1c} was -2.4% in the repaglinide triple therapy group compared to -0.7% (P=0.01) in the metformin plus NPH insulin group and -1.4% in the insulin NPH group. Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (P<0.01). Significant differences in weight gain and hypoglycemia were not seen.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>BID and NPH insulin before dinner</p> <p>vs</p> <p>NPH insulin BID</p>				<p>Secondary: Not reported</p>
<p>Wang et al.⁵⁰ (abstract)</p> <p>Repaglinide 1 mg TID, titrated up to 4 mg TID</p> <p>vs</p> <p>repaglinide 1 mg TID plus metformin 500 mg TID, titrated up to 4 mg TID and 500 mg TID</p>	<p>AC, OL, PG, RCT</p> <p>Patients 18 to 75 years of age with type 2 diabetes, HbA_{1c} >8.5%, BMI ≤35 kg/m², and who were naïve to oral antidiabetic agents,</p>	<p>N=432</p> <p>16 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, two-hour PPG, seven-point plasma glucose, safety</p>	<p>Primary: Mean HbA_{1c} reduction was 4.51±1.64% with combination therapy and 4.05±1.59% with repaglinide. Estimated mean treatment difference for combination therapy vs repaglinide was -0.30% (95% CI, -0.49 to -0.11; P< 0.01).</p> <p>Secondary: Combination therapy demonstrated significant improvements compared to repaglinide in FPG, seven-point plasma glucose, and lunchtime and dinnertime two-hour PPG (P<0.05 for all).</p> <p>Hypoglycemia rates were 2.04 events/patient-year with combination therapy compared to 1.35 events/patient-year with repaglinide (P=0.058). Adverse events were comparable between the two treatments.</p>
<p>Derosa et al.⁵¹ (2009)</p> <p>Nateglinide 60 mg TID and metformin 1,500 to 3,000 mg daily</p> <p>vs</p> <p>glyburide 7.5 to 12.5 mg daily and metformin 1,500 to 3,000 mg daily</p>	<p>DB, MC, PG, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes mellitus, HbA_{1c} >7.0%, BMI 25 to 28 kg/m², and hypertensive (SBP/DBP, >130/≥85 mmHg)</p>	<p>N=248</p> <p>12 months</p>	<p>Primary: Changes in BMI, FPG and PPG, HbA_{1c}, fasting and postprandial plasma insulin, HOMA index, and lipid profile [TC, LDL-C, HDL-C, TG, apolipoprotein A-I, and apolipoprotein B, SBP, and DBP</p> <p>Secondary:</p>	<p>Primary: BMI did not show any significant change during the study.</p> <p>A significant reduction in HbA_{1c} was shown after nine months (P<0.05) and 12 months (P<0.01) in the nateglinide group compared to the baseline value. A significant reduction in HbA_{1c} was seen with glyburide after 12 months (P<0.05) compared to baseline. The HbA_{1c} at 12 months was 6.4% in the nateglinide group compared to 7.3% in the glyburide group (P<0.05).</p> <p>After nine and 12 months, mean FPG levels were significantly decreased in the nateglinide and glyburide groups (P<0.05 and P<0.01, respectively) compared to baseline.</p> <p>Significant changes in PPG were found at nine months (P<0.05) in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	<p>nateglinide group and after 12 months in glyburide and nateglinide groups (P<0.05 and P<0.01, respectively) compared to baseline.</p> <p>Fasting plasma insulin and postprandial insulin did not show any significant change after three, six, nine and 12 months in both groups compared to the baseline.</p> <p>HOMA index decrease was obtained only at 12 months (P<0.05) compared to the baseline value in both groups,</p> <p>No significant change was observed in TC, LDL-C, HDL-C, TG, apolipoprotein A-I, apolipoprotein B, SBP, DBP and heart rate in either group after three, six, nine and 12 months.</p> <p>Secondary: Not reported</p>
<p>Swinnen et al.⁵² (2010)</p> <p>Continuation of secretagogues (sulfonylureas or meglitinides)</p> <p>vs</p> <p>discontinuation of secretagogues (sulfonylureas or meglitinides)</p> <p>All patients received existing metformin regimens and initiated insulin therapy.</p>	<p>PRO</p> <p>Patients 40 to 75 years of age with type 2 diabetes, HbA_{1c} 7.0 to 10.5% receiving oral glucose-lowering drugs</p>	<p>N=865</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: Hypoglycemia, body weight, insulin dose</p>	<p>Primary: In patients continuing secretagogue treatment, HbA_{1c} decreased to 7.0±0.8% at week 12 compared to 7.4±0.9% in patients discontinuing their secretagogues. Endpoint HbA_{1c} level was 7.2±0.9% in both treatment groups. The difference in mean HbA_{1c} reduction during the trial was not significant (-1.59±1.08% for patients continuing secretagogues and -1.30±1.14% for patients discontinuing secretagogues; P=0.382).</p> <p>Secondary: Compared to patients who discontinued secretagogues, patients who continued secretagogues experienced significantly more hypoglycemia (40.0 vs 24.5%; P<0.001) and gained significantly more weight (1.44±3.04 vs 0.43±3.00 kg; P<0.001).</p> <p>End of trial insulin doses, were significantly lower in patients who continued secretagogues compared to patients who discontinued secretagogues (P<0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Black et al.⁵³ (2007)</p> <p>Meglitinide</p> <p>vs</p> <p>meglitinide and metformin</p> <p>vs</p> <p>meglitinide and insulin</p> <p>vs</p> <p>metformin</p> <p>vs</p> <p>placebo</p>	<p>MA (15 trials)</p> <p>Patients with type 2 diabetes</p>	<p>N=3,781</p> <p>Duration varied</p>	<p>Primary: Mortality and morbidity</p> <p>Secondary: Change in HbA_{1c}, weight or BMI, hypoglycemia, adverse effects, quality of life</p>	<p>Primary: No trials reported the effect of meglitinides on mortality and morbidity.</p> <p>Secondary: In the 11 trials comparing meglitinides to placebo, both repaglinide and nateglinide resulted in reductions in HbA_{1c} (0.1 to 2.1% and 0.2 to 0.6%, respectively). In two trials comparing repaglinide to nateglinide, reduction in HbA_{1c} was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in HbA_{1c} compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in HbA_{1c} compared to metformin.</p> <p>Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin.</p> <p>Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides.</p> <p>There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes.</p> <p>There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization DTSQ improved significantly in patients receiving repaglinide compared to patients receiving placebo.</p>
<p>Mearns et al.⁵⁴ (2015)</p>	<p>Network MA (62 RCTs)</p>	<p>N=32,185</p>	<p>Primary: Changes in HbA_{1c},</p>	<p>Primary: All agents significantly reduced HbA_{1c} vs placebo; although, not to the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)	Patients with inadequately controlled type 2 diabetes on metformin alone	3 to 12 months	body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported

*Synonym for glyburide.

†Product not available in the United States.

Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily

Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SR=systematic review, XO=cross-over

Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, DBP=diastolic blood pressure, DTSQ=Diabetes Treatment Satisfaction Questionnaire, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=Glucagon-like peptide-1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HR=hazard ratio, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral protamine Hagedorn, OR=odds ratio, PPG=postprandial plasma glucose, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 10. Relative Cost of the Meglitinides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Nateglinide	tablet	Starlix®*	\$\$\$\$\$	\$\$\$
Repaglinide	tablet	Prandin®*	\$\$\$\$\$	\$
Combination Products				
Repaglinide and metformin	tablet	N/A	N/A	\$\$\$\$\$

*Generic is available in at least one dosage form or strength.

N/A=Not available

X. Conclusions

The meglitinides are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹⁻³ All of the agents are available in a generic formulation.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin (HbA_{1c}) will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The meglitinides are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note that meglitinides are associated

with a limited HbA_{1c}-lowering ability, weight gain, and a greater risk of inducing hypoglycemia compared to other available antidiabetic medications. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/meglitinide, an SGLT2 inhibitor, pioglitazone, or a dipeptidyl peptidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. In addition, guidelines recognize the potential use of meglitinides when postprandial hyperglycemia is present. Among all current clinical guidelines, preference of one meglitinide over another is not stated.⁶⁻¹⁸

The meglitinides have been evaluated in a variety of clinical trials. Three studies have directly compared nateglinide and repaglinide, either as monotherapy or in combination with metformin. In all three studies, the mean change in HbA_{1c} from baseline was significantly greater with repaglinide compared to nateglinide.^{19-20,40} The meglitinides have also been compared to sulfonylureas in monotherapy studies. Glyburide was found to be more effective than nateglinide in one study, whereas glyburide and repaglinide were found to be equally efficacious in another study.²¹⁻²² The combination of nateglinide and metformin was shown to be as effective, or more effective, than the combination of glyburide and metformin in two studies.^{43,51} Several studies evaluated the efficacy of meglitinides in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.^{41-42,45-48}

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the meglitinides.

There is insufficient evidence to support that one brand meglitinide is safer or more efficacious than another within its given indication. Since the meglitinides are not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand meglitinide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Starlix® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2011 Aug.
2. Prandin® [package insert]. Princeton (NJ): Novo Nordisk Inc.; 2017 Feb.
3. Daily Med [database on the internet]. Bethesda (MD): National Library of Medicine; 2017 [cited 2017 Feb]. Available at: <http://dailymed.nlm.nih.gov/dailymed/about.cfm>.
4. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Feb]. Available from: <http://www.thomsonhc.com/>.
5. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc; 2017 [cited Feb 2017]. Available from: <http://online.factsandcomparisons.com>.
6. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2016;39(Suppl. 1):S1–S112.
7. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.
8. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015 Mar;58(3):429-42.
9. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.
10. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1:1-87.
11. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. Endocr Pract. 2016;22(1):84-113.
12. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
13. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
14. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
15. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131(2):364-382.
16. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.
17. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.
18. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care 2014;37(7):2034-2054.
19. Rosenstock J, Hassman D, Madder R, et al. Repaglinide versus nateglinide monotherapy a randomized, multicenter study. Diabetes Care. 2004;27(6):1265-70.
20. Li J, Tian H, Li Q et al. Improvement of insulin sensitivity and β -cell function by nateglinide and repaglinide in type 2 diabetic patients – a randomized controlled double-blind and double-dummy multicentre clinical trial. Diabetes Obes Metab. 2007;9(4):558-65.

21. Hollander P, Schwartz S, Gatlin M, et al. Importance of early insulin secretion comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. *Diabetes Care*. 2003;24(6):983-8.
22. Wolffenbittel B, Landgraf R. A 1-year Multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care*. 1999;22(3):463-7.
23. Derosa G, Mugellini A, Ciccarelli L, et al. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. *Clin Ther*. 2003;25(2):472-84.
24. Cesur M, Corapcioglu D, Gursoy A, Gonen S, Ozduman M, Emral R, et al. A comparison of glycemic effects of glimepiride, repaglinide, and insulin glargine in type 2 diabetes mellitus during Ramadan fasting. *Diabetes Res Clin Pract*. 2007 Feb;75(2):141-7.
25. Taki H, Maki T, Iso T, Tanabe S, Kajiura T. Postmarketing study of nateglinide in Japan: treatment of medication-naïve patients with type 2 diabetes. *Adv Ther*. 2005 Nov-Dec;22(6):621-35.
26. Taki H, Maki T, Iso T, Iwamoto K, Kajiura T. Study of nateglinide in Japan: long-term treatment of patients with type 2 diabetes. *Adv Ther*. 2006 Mar-Apr;23(2):307-24.
27. Schwarz SL, Gerich JE, Marcellari A, et al. Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naïve elderly patients with type 2 diabetes. *Diabetes Obes Metab*. 2008; 10(8): 652-60.
28. Zhou J, Li H, Zhang X, Peng Y, et al. Nateglinide and acarbose are comparably effective reducers of postprandial glycemic excursions in Chinese antihyperglycemic agent-naïve subjects with type 2 diabetes. *Diabetes Technology & Therapeutics* 2013;15(6):481-488.
29. Chisalita SI, Lindström T, Eson Jennersjö P, Paulsson JF, Westermark GT, Olsson AG, Arnqvist HJ. Differential lipid profile and hormonal response in type 2 diabetes by exogenous insulin aspart versus the insulin secretagogue repaglinide, at the same glycemic control. *Acta Diabetol*. 2009 Mar;46(1):35-42. Epub 2008 Sep 6.
30. Lund SS, Tarnow L, Stehouwer CD, Schalkwijk CG, Teerlink T, Gram J, Winther K, Frandsen M, Smidt UM, Pedersen O, Parving HH, Vaag AA. Impact of metformin versus repaglinide on non-glycaemic cardiovascular risk markers related to inflammation and endothelial dysfunction in non-obese patients with type 2 diabetes. *Eur J Endocrinol*. 2008 May;158(5):631-41.
31. Lund SS, Tarnow L, Frandsen M, Smidt UM, Pedersen O, Parving HH, Vaag AA. Impact of metformin versus the prandial insulin secretagogue, repaglinide, on fasting and postprandial glucose and lipid responses in non-obese patients with type 2 diabetes. *Eur J Endocrinol*. 2008 Jan;158(1):35-46.
32. Fang FS, Gong YP, Li CL, Li J, et al. Comparison of repaglinide and metformin monotherapy as an initial therapy in Chinese patients with newly diagnosed type 2 diabetes mellitus. *European Journal of Endocrinology* 2014;170:901-908.
33. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med*. 2007 Sep 18;147(6):386-9.
34. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract*. 2008 Feb;79(2):196-203.
35. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2005 Jul 20;(3):CD002966.
36. Gangji AS, Cukierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care*. 2007;30(2):389-94.
37. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007 Jul 18;(3):CD006063.
38. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2006 Oct 18;(4):CD006060.
39. Kheirbek RE, Alemi F, Zargoush M. Comparative effectiveness of hypoglycemic medications among veterans. *J Manag Care Pharm*. 2013;19(9):740-44.
40. Raskin P, Klaff L, Mill J, et al. Efficacy and safety of combination therapy repaglinide plus metformin versus nateglinide plus metformin. *Diabetes Care*. 2003;26(7):2063-8.
41. Horton E, Clinkingbeard C, Gatlin M, et al. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care*. 2000;23(11):1660-5.
42. Marre M, Van Gaal L, Usadel K-H, et al. Nateglinide improves glycemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. *Diabetes Obes Metab*. 2002;4(3):177-86.

43. Gerich J, Raskin P, Jean-Louis L, et al. PRESERVE- β Two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. *Diabetes Care*. 2003;28(9):2093-9.
44. Schwarz SL, Gerich JE, Marcellari A, et al. Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naïve elderly patients with type 2 diabetes. *Diabetes Obes Metab*. 2008; 10(8): 652-60.
45. Fonseca V, Grunberger G, Gupta S, et al. Addition of nateglinide to rosiglitazone monotherapy suppresses mealtime hyperglycemia and improved overall glycemic control. *Diabetes Care*. 2003;26(6):1685-90.
46. Moses R, Slobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 1999;22(1):119-24.
47. Raskin P, Mill J, Saad MF, et al. Combination therapy for type 2 diabetes: repaglinide plus rosiglitazone. *Diabet Med*. 2004;21(4):329-35.
48. Ozbek M, Erdogan M, Karadeniz M, Cetinkalp S, Ozgen AG, Saygili F et al. Preprandial repaglinide decreases exogenous insulin requirements and A1C levels in type 2 diabetic patients taking intensive insulin treatment. *Acta Diabetol*. 2006 Dec;43(4):148-51.
49. Civera M, Merchante A, Salvador M, Sanz J, Martínez I. Safety and efficacy of repaglinide in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes. *Diabetes Res Clin Pract*. 2008 Jan;79(1):42-7. Epub 2007 Aug 21.
50. Wang W, Bu R, Su Q, Liu J, Ning G. Randomized study of repaglinide alone and in combination with metformin in Chinese subjects with type 2 diabetes naïve to oral antidiabetes therapy (abstract). *Expert Opin Pharmacother*. 2011 Dec;12(18):2791-9.
51. Derosa G, D'Angelo A, Fogari E, et al. Nateglinide and glibenclamide metabolic effects in naïve type 2 diabetic patients treated with metformin. *J Clin Pharm Ther* 2009;34: 13-23.
52. Swinnen SG, Dain MP, Mauricio D, DeVries JH, Hoeksra JB, Holleman F. Continuation vs discontinuation of insulin secretagogues when initiating insulin in type 2 diabetes. *Diabetes, Obesity and Metabolism*. 2010;12:923-5.
53. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogs for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):CD004654.
54. Mearns ES, Sobieraj DM, White CM, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One*. 2015 Apr 28;10(4):e0125879.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Sodium-glucose Cotransport 1 Inhibitors
AHFS Class 682017
May 10, 2017**

I. Overview

Currently there are no prescription medications classified by American Hospital Formulary Service (AHFS) as Sodium-glucose Cotransport 1 Inhibitors.

II. Conclusions

There are no prescription medications available in the sodium-glucose cotransport 1 inhibitors class (AHFS Class 682017).

III. Recommendations

No sodium-glucose cotransport 1 inhibitor is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 682017 in the Preferred Drug List screening process. If new prescription sodium-glucose cotransport 1 inhibitors are added, it is recommended that this class be re-reviewed.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Sodium-glucose Cotransport 2 Inhibitors
AHFS Class 682018
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Sodium-glucose cotransport 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents recently approved by the Food and Drug Association (FDA). The kidneys play a pivotal role in controlling plasma glucose concentration, reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is reabsorbed in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.^{1,2}

SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, including weight loss and small decreases in systolic and diastolic blood pressure as observed during clinical trials.¹⁻¹²

Several new agents have been included since the last review, including empagliflozin (Jardiance[®]) and several combination products (dapagliflozin and empagliflozin with metformin, empagliflozin with linagliptin, and canagliflozin with metformin extended-release). All of the SGLT2 inhibitors are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.³⁻¹³ Empagliflozin is also indicated to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. Empagliflozin was studied in a postmarket clinical trial of more than 7,000 patients with type 2 diabetes and cardiovascular disease. In the trial, empagliflozin was shown to reduce the risk of cardiovascular death compared to a placebo when added to standard of care therapies for diabetes and atherosclerotic cardiovascular disease.^{7,13}

The sodium-glucose cotransport 2 inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available. This class was last reviewed in February 2015.

Table 1. Sodium-glucose Cotransport 2 Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Canagliflozin	tablet	Invokana [®]	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dapagliflozin	tablet	Farxiga®	none
Empagliflozin	tablet	Jardiance®	none
Combination Products			
Canagliflozin and Metformin	extended-release tablet, tablet	Invokamet®, Invokamet XR®	none
Dapagliflozin and Metformin	extended-release tablet	Xigduo XR®	none
Empagliflozin and Linagliptin	tablet	Glyxambi®	none
Empagliflozin and Metformin	tablet	Synjardy®	none

PDL=Preferred Drug List

II. Evidence- Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Sodium-glucose Cotransport 2 Inhibitors

Clinical Guideline	Recommendation(s)
American Diabetes Association: Standards of Medical Care in Diabetes (2016) ¹⁴	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <p>Prevention or delay of type 2 diabetes</p> <ul style="list-style-type: none"> An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus. Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p>Glycemic goals in adults</p> <ul style="list-style-type: none"> Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose

Clinical Guideline	Recommendation(s)
	<p>monitoring, and effective doses of multiple glucose-lowering agents including insulin.</p> <p><u>Pharmacologic therapy for type 1 diabetes</u></p> <ul style="list-style-type: none"> • Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. • Most patients should use of insulin analogs to reduce hypoglycemia risk. • Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. <p><u>Pharmacologic therapy for type 2 diabetes</u></p> <ul style="list-style-type: none"> • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If the A_{1c} target is not achieved after approximately three months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • Pregestational Diabetes <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1c} <6.5%, to reduce the risk of congenital anomalies. ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. • Gestational Diabetes Mellitus <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. • General Principles for Management of Diabetes in Pregnancy <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using

Clinical Guideline	Recommendation(s)
	<p>reliable contraception.</p> <ul style="list-style-type: none"> ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. • Due to increased red blood cell turnover, A_{1C} is lower in normal pregnancy than in normal nonpregnant women. The A_{1C} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012 and 2015 Update)^{15,16}</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more

Clinical Guideline	Recommendation(s)						
	<p>likely insulin will be required.</p> <ul style="list-style-type: none"> On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. 						
Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations							
Initial Drug Monotherapy		Metformin					
Efficacy (↓HbA _{1c})		High					
Hypoglycemia		Low risk					
Weight		Neutral/loss					
Side Effects		Gastrointestinal/lactic acidosis					
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)							
Two Drug Combinations	Metformin + sulfonyl-urea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)	
Efficacy (↓HbA _{1c})	High	High	Intermediate	Intermediate	High	Highest	
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk	
Weight	Gain	Gain	Neutral	Loss	Loss	Gain	
Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia	
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)							
Three Drug Combinations	Metformin + sulfonyl-urea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + SGLT2 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +	
	TZD, DPP-4 inhibitor, SGLT2 inhibitor,	Sulfonyl-urea, DPP-4 inhibitor, SGLT2	Sulfonyl-urea, TZD, SGLT2 inhibitor,	Sulfonyl-urea, TZD, DPP-4 inhibitor,	Sulfonyl-urea, TZD, or insulin	TZD, DPP-4 inhibitor, SGLT2 inhibitor,	

Clinical Guideline	Recommendation(s)						
		GLP-1 receptor agonist, or insulin	inhibitor, GLP-1 receptor agonist, or insulin	or insulin	or insulin		or GLP-1 receptor agonist
	If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents						
	More Complex Insulin Strategies	Combination injectable therapy					
American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012) ¹⁷	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. 						
American Association of Clinical Endocrinologists/ American College Of Endocrinology: Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015) ¹⁸	<p>Antihyperglycemic pharmacotherapy for type 2 diabetes</p> <ul style="list-style-type: none"> The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement. Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is 						

Clinical Guideline	Recommendation(s)
	<p>flexible and is recommended for intensive insulin therapy.</p> <ul style="list-style-type: none"> Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists: Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm 2016 (2016)¹⁹</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. The therapeutic regimen should be as simple as possible to optimize adherence. <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> GLP-1 receptor agonists. Sodium glucose cotransporter 2 (SGLT-2) inhibitors. DPP-4 inhibitors. . TZDs (use with caution). Alpha-glucosidase inhibitors. sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus:

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ DPP-4 inhibitors. ○ TZD. ○ Basal insulin. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p>Three-drug combination therapy</p> <ul style="list-style-type: none"> ● Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. ● Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. ● Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of reaching target with a third agent. ● Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. ● Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. ● Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p>Insulin therapy algorithm</p> <ul style="list-style-type: none"> ● Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. ● Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. ● Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. ● Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <p>Basal insulin</p> <ul style="list-style-type: none"> ● Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. ● Titrate insulin dose every two to three days to reach glycemic goals. ● Basal insulin analogues (glargine and detemir) are preferred over protamine

Clinical Guideline	Recommendation(s)
	<p>Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection.</p> <ul style="list-style-type: none"> Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p><u>Basal-bolus insulin regimens</u></p> <ul style="list-style-type: none"> Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. Doses of insulin may be titrated every two to three days to reach glycemic goals. <p><u>Basal insulin and incretin therapy regimens</u></p> <ul style="list-style-type: none"> Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last updated July 2016)²⁰</p>	<p><u>Individualized care</u></p> <ul style="list-style-type: none"> Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective. Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p><u>HbA_{1c} targets</u></p> <ul style="list-style-type: none"> Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> reinforce advice about diet, lifestyle and adherence to drug treatment and support the person to aim for an HbA_{1c} level of 7.0% and intensify drug treatment. Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of

Clinical Guideline	Recommendation(s)
	<p>falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job</p> <ul style="list-style-type: none"> ○ for whom intensive management would not be appropriate, for example, people with significant comorbidities. <ul style="list-style-type: none"> ● If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p><u>Drug treatment</u></p> <ul style="list-style-type: none"> ● For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost ● If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. ● Initial drug treatment <ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m²: <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p><u>First intensification of drug treatment</u></p> <ul style="list-style-type: none"> ● In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. ● In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. ● Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes. <p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> ● In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment. ● If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. ● Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in six months). ● In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment. ● In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. ● Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p>Insulin-based treatments</p> <ul style="list-style-type: none"> ● When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. • Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation. ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: <ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals. ○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes: <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. • Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). • Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)²¹</p>	<ul style="list-style-type: none"> • Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. ● A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. ● Recommend education and self-management, as appropriate. ● Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. ● Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes (2012)²²</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> ● Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. ● Match the timing of medication (including insulin) and meals. ● Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. ● Introduce physical activity gradually, based on the individual’s willingness and ability, and setting individualized and specific goals. ● Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. ● Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> ● Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. ● A lower HbA_{1c} target may be considered if it is easily and safely achieved. ● A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> ● Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. ● Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. ● First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some

Clinical Guideline	Recommendation(s)
	<p>populations; these agents can also be used initially where metformin cannot.</p> <ul style="list-style-type: none"> ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. ● Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. ● Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. ● Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering medications (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> ● Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. ● Provide education and appropriate self-monitoring. ● Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. ● Continue metformin. Other oral agents may also be continued. ● Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). ● Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. ● Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). ● Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)²³</p>	<ul style="list-style-type: none"> ● Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations ≥ 250 mg/dL. ○ Whose HbA_{1c} is >9%. ● In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. ● Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. ● Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. ● Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. ● Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
<p>National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November 2016)²⁴</p>	<p>Education and information for children and young people with type 1 diabetes</p> <ul style="list-style-type: none"> ● Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. ● Tailor the education programme to each child or young person with type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. ● Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. ● Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. ● Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. ● Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. ● Encourage children and young people with type 1 diabetes to wear or carry something that identifies them as having type 1 diabetes (e.g., a bracelet). ● Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. ● Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations. • Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p><u>Insulin therapy for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. • Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen. • Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. • Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. • Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. • Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin infusion users. • Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. • Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin

Clinical Guideline	Recommendation(s)
	<p>(0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%.</p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. • Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. • Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with type 1 diabetes a review of injection sites at each clinic visit. • Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. • If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily injections, continuous subcutaneous insulin infusion [CSII or insulin pump] therapy or once-, twice- or three-times daily mixed insulin injections). <p><u>Oral medicines for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. <p><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. • Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. • Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. • Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain. <p><u>Education and information for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ HbA_{1c} monitoring and targets ○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control ○ the aims of metformin therapy and possible adverse effects

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ the complications of type 2 diabetes and how to prevent them. ● Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. ● Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every 2 years. ● Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. ● Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. ● Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible government disability benefits. ● Take particular care when communicating with and providing information to children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. <p><u>Dietary management for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> ● At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. ● Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. ● At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. ● Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications. ● Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. ● Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. ● At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. • Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy. <p><u>Metformin</u></p> <ul style="list-style-type: none"> • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management (Published 2015; last updated July 2016)²⁵</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> • Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. • Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target. • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles ○ total glycated hemoglobin estimation (if abnormal hemoglobins). • Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. • Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia. • Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p><u>Self-monitoring of blood glucose</u></p> <ul style="list-style-type: none"> • Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least four times a day, including before each meal and before bed. • Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). • Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia. • Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. • Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy)

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking. <p><u>Continuous glucose monitoring</u></p> <ul style="list-style-type: none"> • Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. • Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause. ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level ≥9%) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in HbA_{1c} of 2.5% or more. • For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. <p><u>Insulin regimens</u></p> <ul style="list-style-type: none"> • Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. • Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only). <p><u>Long-acting insulin</u></p> <ul style="list-style-type: none"> • Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. • Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul style="list-style-type: none"> ○ an existing insulin regimen being used by the person that is achieving their agreed targets ○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. • Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p><u>Rapid-acting insulin</u></p> <ul style="list-style-type: none"> • Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. • Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. • If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin.

Clinical Guideline	Recommendation(s)
	<p><u>Mixed insulin</u></p> <ul style="list-style-type: none"> Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p><u>Optimizing insulin therapy</u></p> <ul style="list-style-type: none"> For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously optimized insulin regimen, the following should be considered: <ul style="list-style-type: none"> injection technique injection sites self-monitoring skills knowledge and self-management skills nature of lifestyle psychological and psychosocial difficulties possible organic causes such as gastroparesis. Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. <p><u>Adjuncts</u></p> <ul style="list-style-type: none"> Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Check injection site condition at least annually and if new problems with blood glucose control occur.
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. If adults with type 1 diabetes choose to drink alcohol, they should be advised to

Clinical Guideline	Recommendation(s)
<p>Association (2014)²⁶</p>	<p>do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated.</p> <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <p><u>Glycemic control goals</u></p> <ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the sodium-glucose cotransport 2 inhibitors are noted in Table 3.

Table 3. FDA-Approved Indications for the Single-Entity Sodium-glucose Cotransport 2 Inhibitors³⁻⁷

Indication	Canagliflozin	Dapagliflozin	Empagliflozin
Type 2 diabetes mellitus, an adjunct to diet and exercise to improve glycemic control	✓	✓	✓
To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease			✓

Table 4. FDA-Approved Indications for the Combination Sodium-glucose Cotransport 2 Inhibitors^{3,4,8-12}

Indication	Canagliflozin and Metformin	Dapagliflozin and Metformin	Empagliflozin and Linagliptin	Empagliflozin and Metformin
Type 2 diabetes mellitus, as an adjunct to diet and exercise to improve glycemic control in adults when treatment with both agents is appropriate	✓	✓	✓	✓

IV. Pharmacokinetics

The pharmacokinetic parameters of the sodium-glucose cotransport 2 inhibitors are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Sodium-glucose Cotransport 2 Inhibitors³

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Canagliflozin	65	99 (primarily albumin)	Liver (extensive)	Urine (33) Feces (41.5)	10.6 to 13.1
Dapagliflozin	78	91	Liver (extensive)	Urine (75) Feces (21)	8 to 12.9
Empagliflozin	Not reported	86.2	Glucuronidation	Urine (54.4) Feces (41.2)	12.4
Combination Products					
Canagliflozin and Metformin	65/ 50 to 60	99 (primarily albumin)/ Negligible (% not reported)	Liver (extensive)/ None	Urine (33) Feces (41.5)/ Renal (90)	10.6 to 13.1/ 6.2
Dapagliflozin and Metformin	78/ 50 to 60	91/ Negligible (% not reported)	Liver (extensive)/ None	Urine (75) Feces (21)	8 to 12.9/ 6.2

		reported)		Renal (90)	
Empagliflozin and Linagliptin	Not reported/ 30	86.2/ 70 to 99	Glucuronidation/ Limited	Urine (54.4) Feces (41.2)/ Urine (5 to 7) Bile (80)	12.4/ >100
Empagliflozin and Metformin	Not reported/ 50 to 60	86.2/ Negligible (% not reported)	Glucuronidation/ None	Urine (54.4) Feces (41.2)/ Renal (90)	12.4/ 6.2

V. Drug Interactions

There are no significant drug interactions reported with canagliflozin, dapagliflozin, or empagliflozin.^{3,4} Coadministration of canagliflozin with UDP-glucuronosyltransferase inducers, such as rifampin, may decrease the exposure to canagliflozin and therefore decrease efficacy.⁵ Additionally, Coadministration of canagliflozin with digoxin may increase digoxin exposure. Use caution if concomitant use is required and monitor digoxin levels. Consider advising the patient to report signs or symptoms of digoxin toxicity.⁵

VI. Adverse Drug Events

The most common adverse drug events reported with the sodium-glucose cotransport 2 inhibitors are listed in Tables 6 and 7. The boxed warning for canagliflozin-metformin is listed in Table 8.

Table 6. Adverse Drug Events (%) Reported with the Single-Entity SGLT2 Inhibitors⁴

Adverse Event	Canagliflozin	Dapagliflozin	Empagliflozin
Central Nervous System			
Fatigue	2.0 to 2.2	-	-
Gastrointestinal			
Abdominal pain	1.7 to 1.8	-	-
Constipation	1.8 to 2.3	2	-
Nausea	2.2 to 2.3	3	2
Genitourinary			
Dysuria	-	2	-
Fungal vaginosis†	-	7 to 8	-
Genitourinary fungal infection‡	10.4 to 11.4 (female) 3.7 to 4.2 (male)	7 to 8 (female) 3 (male)	5 to 6 (female) 2 to 3 (male)
Increased urination§	4.6 to 5.3	3 to 4	3
Urinary tract infection§§	4.3 to 5.9	4 to 6	9
Vulvovaginal pruritus	1.6 to 3	-	-
Endocrine and metabolic			
Dyslipidemia	-	2 to 3	4
Hypovolemia*	-	1	✓
Increased LDL cholesterol	✓	✓	5 to 7
Increased serum phosphate	✓	2	-
Renal			
Decreased estimated GFR	✓	✓	✓
Increased serum creatinine	✓	✓	✓
Other			
Back pain	-	3 to 4	-
Hypersensitivity reaction	3.8 to 4.2	✓	-
Increased hematocrit	-	1	3 to 4
Increased hemoglobin	✓	-	-
Influenza	-	2 to 3	-

Adverse Event	Canagliflozin	Dapagliflozin	Empagliflozin
Ketoacidosis	-	-	✓
Limb pain	-	2	✓
Nasopharyngitis	-	6 to 7	✓
Thirst	2.3 to 2.8	-	2
Urticaria	-	✓	✓

*Hypovolemia includes: dehydration, hypovolemia, orthostatic hypotension, and hypotension.

†Fungal vaginosis includes: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, vaginitis bacterial.

‡Genitourinary fungal infections include: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, posthitis.

§Increased urination includes: polyuria, pollakiuria, urine output increased, micturition urgency, and nocturia.

§§Urinary tract infection includes: urinary tract infection, cystitis, kidney infection, and urosepsis.

-Incidence not reported or <1%.

✓ Incidence not specified.

Table 7. Adverse Drug Events (%) Reported with the Combination Product SGLT2 Inhibitors⁴

Adverse Event	Canagliflozin and Metformin [#]	Dapagliflozin and Metformin	Empagliflozin and Linagliptin	Empagliflozin and Metformin
Central Nervous System				
Dizziness	-	3	✓	✓
Fatigue	2.0 to 2.2	✓	✓	✓
Headache	-	5	✓	✓
Gastrointestinal				
Abdominal pain	1.7 to 1.8	✓	✓	✓
Constipation	1.8 to 2.3	3	✓	✓
Nausea	2.2 to 2.3	3 to 4	2	2
Genitourinary				
Dysuria	-	2	✓	✓
Fungal vaginosis [†]	-	✓	✓	✓
Genitourinary fungal infection [‡]	10.4 to 11.4 (female) 3.7 to 4.2 (male)	9 (female) 4 (male)	5 to 6 (female) 2 to 3 (male)	5 to 6 (female) 2 to 3 (male)
Increased urination [§]	4.6 to 5.3	2 to 3	3	3
Urinary tract infection ^{§§}	4.3 to 5.9	6	11 to 13	9
Vulvovaginal pruritus	1.6 to 3	✓	✓	✓
Endocrine and metabolic				
Dyslipidemia	-	2 to 3	4	4
Hypovolemia [*]	-	✓	✓	✓
Increased LDL cholesterol	✓	✓	✓	5 to 7
Increased serum phosphate	✓	✓	✓	✓
Renal				
Decreased estimated GFR	✓	✓	✓	✓
Increased serum creatinine	✓	✓	✓	✓
Other				
Back pain	-	✓	✓	✓
Cough	-	3	✓	✓
Hypersensitivity reaction	3.8 to 4.2	✓	✓	✓
Increased hematocrit	-	✓	✓	3 to 4
Increased hemoglobin	✓	✓	✓	✓
Influenza	-	3 to 4	✓	✓
Ketoacidosis	-	✓	✓	✓
Limb pain	-	✓	✓	✓
Nasopharyngitis	-	✓	6 to 7	✓
Pharyngitis	-	2 to 3	✓	✓
Thirst	2.3 to 2.8	✓	2	2

Adverse Event	Canagliflozin and Metformin [#]	Dapagliflozin and Metformin	Empagliflozin and Linagliptin	Empagliflozin and Metformin
Upper respiratory tract infection	-	‡	7	‡
Urticaria	-	‡	‡	‡

*Hypovolemia includes: dehydration, hypovolemia, orthostatic hypotension, and hypotension.

†Fungal vaginosis includes: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, vaginitis bacterial.

‡Genitourinary fungal infections include: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, posthitis.

§Increased urination includes: polyuria, pollakiuria, urine output increased, micturition urgency, and nocturia.

§§Urinary tract infection includes: urinary tract infection, cystitis, kidney infection, and urosepsis.

-Incidence not reported or <1%.

✓ Incidence not specified.

[#]The incidence and type of adverse reactions for the combination canagliflozin/metformin was similar to the adverse reactions of canagliflozin alone. There were no additional adverse reactions identified in the pooling of three additional placebo-controlled studies that included metformin relative to the four placebo-controlled studies used for canagliflozin alone.

Table 8. Boxed Warning for the Metformin-Containing Combination Products⁵

WARNING	
<u>Lactic Acidosis:</u>	
<ul style="list-style-type: none"> • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. • Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. • Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information. • If metformin-associated lactic acidosis is suspected, immediately discontinue metformin-containing products and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. 	

VII. Dosing and Administration

The usual dosing regimens for the sodium-glucose cotransport 2 inhibitors are listed in Table 9.

Table 9. Usual Dosing Regimens for the Sodium-glucose Cotransport 2 Inhibitors³⁻¹²

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Canagliflozin	<u>Type 2 diabetes mellitus:</u> Tablet: initial, 100 mg once daily before the first meal of the day; in patients tolerating canagliflozin who have an eGFR \geq 60 mL/min/1.73 m ² and require additional glycemic control, the dose can be increased to 300 mg once daily	Safety and efficacy in children have not been established.	Tablet: 100 mg 300 mg
Dapagliflozin	<u>Type 2 diabetes mellitus:</u> Tablet: initial, 5 mg once daily in the morning; in patients tolerating dapagliflozin who require additional glycemic control, the dose can be increased to 10 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Empagliflozin	Type 2 diabetes mellitus, to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease : Tablet: 10 mg once daily in the morning; in patients tolerating empagliflozin who require additional glycemic control, the dose can be increased to 25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 10 mg 25 mg
Combination Products			
Canagliflozin and Metformin	Type 2 diabetes mellitus: Extended-release tablet: initial, based on current regimen once daily in the morning with food; adjust to a maximum of 300-2,000 mg Tablet: initial, based on current regimen start canagliflozin 50 mg and/or metformin 500 mg twice daily with meals	Safety and efficacy in children have not been established.	Extended-release tablet: 50-500 mg 50-1,000 mg 150-500 mg 150-1,000 mg Tablet: 50-500 mg 50-1,000 mg 150-500 mg 150-1,000 mg
Dapagliflozin and Metformin	Type 2 diabetes mellitus: Extended-release tablet: initial, based on current regimen once daily in the morning with food; adjust to a maximum of 10-2,000 mg	Safety and efficacy in children have not been established.	Extended-release tablet: 5-500 mg 5-1,000 mg 10-500 mg 10-1,000 mg
Empagliflozin and Linagliptin	Type 2 diabetes mellitus: Tablet: initial, 10-5 mg once daily in the morning with or without food; in patients tolerating initial dose, may increase to 20-5 mg	Safety and efficacy in children have not been established.	Tablet: 10-5 mg 25-5 mg
Empagliflozin and Metformin	Type 2 diabetes mellitus: Tablet: initial, based on current regimen twice daily with meals; adjust to a maximum of 25-2,000 mg	Safety and efficacy in children have not been established.	Tablet: 5-500 mg 5-1,000 mg 12.5-500 mg 12.5-1,000 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the sodium-glucose cotransport 2 inhibitors are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Sodium-glucose Cotransport 2 Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
<p>Stenlof et al.²⁷ (2013) DIA3005</p> <p>Canagliflozin 100 mg QD</p> <p>vs</p> <p>canagliflozin 300 mg QD</p> <p>vs</p> <p>placebo</p> <p>Patients received metformin rescue if FPG was >270 mg/dL after day 1 to week 6; >240 mg/dL after week 6 to week 12; or >200 mg/dL after week 12 to week 26.</p> <p>A substudy was conducted for patients with hyperglycemia.</p>	<p>AC, DB, MC, PC, RCT</p> <p>Patients ≥18 and <80 years of age with T2DM, FPG <270 mg/dL and no antihyperglycemic therapy and an HbA_{1c} ≥7.0 and <10.0% or prior metformin plus sulfonylurea combination therapy and an HbA_{1c} ≥6.5 and <9.5%</p>	<p>N=584 (N=91 enrolled in the hyperglycemic substudy)</p> <p>26 weeks followed by a 26 week ES using active control (sitagliptin)</p>	<p>Primary: Change in HbA_{1c} level from baseline to week 26</p> <p>Secondary: Proportion of patients with HbA_{1c} <7.0%, change in FPG, PPG and systolic blood pressure, percent change in body weight, triglyceride level, HDL-C, apolipoprotein B and safety endpoints</p>	<p>Primary: At the end of treatment, the 100 and 300 mg QD doses resulted in a statistically significant improvement in HbA_{1c} (-1.03 and -0.77 vs 0.14%, respectively; P<0.001 for both doses) compared to placebo.</p> <p>Secondary: Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0% (45 and 62 vs 21%, respectively; P<0.01), significant reductions of FPG (-27 and -35 vs 8 mg/dL, respectively; P<0.01), significant reductions of PPG (-43 and -59 vs 5 mg/dL, respectively; P<0.01), and in percent body weight reduction compared to placebo (-2.8 and -3.9 kg, respectively; P<0.01).</p> <p>From baseline, with the 100 and 300 mg doses, there were decreases in systolic blood pressure (-3.7 and -5.4 mm Hg, respectively) and increases in HDL-C (11.2 and 10.6 vs 4.5 mg/dL, respectively; P<0.01) relative to placebo. There was also a significantly smaller increase from baseline in triglycerides, including a decrease with the 300 mg dose (2.5 and -2.3 vs 7.9 mg/dL, respectively; P<0.01).</p> <p>In a subset of patients with samples sufficient for analysis (n=349), greater increases in apolipoprotein B levels were seen with canagliflozin 100 (1.2%) and 300 mg (3.5%) than with placebo (0.9%).</p> <p>Urinary tract infections, genital mycotic infections, and adverse events related to osmotic diuresis and reduced intravascular volume occurred at higher rates with both doses of canagliflozin than with placebo.</p> <p>The incidence of documented hypoglycemic episodes prior to rescue therapy was similar between the treatment groups (canagliflozin 100 mg, 3.6%; canagliflozin 300 mg, 3.0%; placebo, 2.6%), and no severe</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>These patients were not allowed to receive placebo.</p> <p>Following completion of the study, patients randomized to receive placebo were transitioned to therapy with sitagliptin.</p>				<p>hypoglycemic episodes were reported.</p> <p>Efficacy was maintained throughout the 52 week study period and the adverse event profile was similar through the 26 week extension period of the study.</p>
<p>Bode et al.²⁸ (abstract) (2013)</p> <p>Canagliflozin 100 mg QD</p> <p>vs</p> <p>canagliflozin 300 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients 55 to 80 years of age with T2DM, an HbA_{1c} ≥7.0 and <10% despite treatment with blood glucose lowering therapy</p>	<p>N=716</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c} level from baseline to week 26</p> <p>Secondary: Proportion of patients with HbA_{1c} <7.0%, change in FPG, and systolic blood pressure, percent change in body weight, triglyceride level, and HDL-C</p>	<p>Primary: At 26 weeks, significant reductions in HbA_{1c} were observed in all canagliflozin treatment groups compared placebo (-0.60 and -0.73% for canagliflozin 100 and 300 mg QD respectively vs -0.03% for placebo; P<0.001 for all doses).</p> <p>Secondary: At 26 weeks, a greater proportion of patients achieved an HbA_{1c} <7.0% with canagliflozin compared to placebo (percent not reported; P<0.001)</p> <p>At week 26, greater reductions in FPG, systolic blood pressure, and increased HDL-C levels were observed with canagliflozin vs placebo (P<0.001).</p>
<p>Ferranini et al.²⁹ (2010)</p> <p>Dapagliflozin 2.5 mg QD</p> <p>vs</p> <p>dapagliflozin 5 mg</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately</p>	<p>N=485</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1c}</p> <p>Secondary: Change from baseline in FPG and body weight and safety</p>	<p>Primary: At week 24, dapagliflozin 5 and 10 mg QAM provided significant improvements in HbA_{1c} compared to placebo (0.8%, -0.9% vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons).</p> <p>Secondary: Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg QAM comparison compared to placebo (P<0.05 for both comparisons).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>QD vs dapagliflozin 10 mg QD vs placebo</p> <p>Patients were divided into QAM and QPM dosing cohorts. In addition, those with HbA_{1c} >10.0 and ≤12.0% were evaluated separately in a high HbA_{1c} cohort. The QAM dosing cohort was used for evaluation of primary and secondary endpoints.</p>	<p>controlled blood sugar, BMI ≤45 kg/m² and fasting C-peptide ≥1.0 ng/mL</p>		<p>assessments</p>	<p>Changes in HbA_{1c} and FPG for the 2.5 mg arm and changes in weight for all three comparisons also favored the treatment arm; however differences were not considered significant.</p> <p>In both exploratory cohorts (QAM dosing and high HbA_{1c}), dapagliflozin had greater reductions in primary and secondary analyses compared to placebo. However, in the high HbA_{1c} cohort the reduction compared to placebo was considered numerically greater.</p> <p>Treatment with dapagliflozin did not result in any clinically meaningful changes from baseline in serum electrolytes, serum albumin or renal function.</p> <p>Signs, symptoms, and other reports suggestive of urinary tract infections and genital infection were more frequently noted in the dapagliflozin arms.</p> <p>There were no major episodes of hypoglycemia.</p>
<p>Bailey et al.³⁰ (2012)</p> <p>Dapagliflozin 1 mg QD vs dapagliflozin 2.5 mg QD</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately controlled blood</p>	<p>N=282 24 weeks</p>	<p>Primary: Change from baseline in HbA_{1c}</p> <p>Secondary: Change from baseline in FPG and body weight, glucose after two hour liquid meal,</p>	<p>Primary: At week 24, dapagliflozin 1, 2.5 and 5 mg QD provided significant improvements in HbA_{1c} compared to placebo (-0.7%, -0.7%, -0.8% vs 0.2%, respectively; P<0.05 for all comparisons).</p> <p>Secondary: Changes in FPG and body weight and glucose after two hour liquid meal were significantly lower in the dapagliflozin arms compared to placebo (P<0.05 for all comparisons). The change in percentage of patients with HbA_{1c} <7.0% was greater in the dapagliflozin arms; however only the 1</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dapagliflozin 5 mg QD vs placebo	sugar, BMI ≤ 45 kg/m ² and fasting C-peptide ≥ 0.34 ng/mL		percentage of patients with HbA _{1c} <7.0% and safety assessments	mg QD arm was considered significantly greater than placebo (53.6 vs 24.6%, respectively; P<0.05). No major episodes of hypoglycemia were reported during the study, and frequency of minor episodes was similar for dapagliflozin and placebo groups. No clinically meaningful changes were observed in serum electrolytes, serum albumin, or renal function parameters.
Bailey et al. ³¹ (2015) Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo After 24 weeks, low-dose double-blind metformin 500 mg/day was added to the placebo group regimen.	DB, PC, RCT Patients with type 2 diabetes 18 to 77 years of age and inadequate glycaemic control on diet and exercise (HbA _{1c} 7.0 to 10.0%)	N=274 102 weeks	Primary: Change from baseline in HbA _{1c} over 102 weeks, FPG, body weight, percentage of patients achieving HbA _{1c} <7.0% Secondary: Not reported	Primary: At 102 weeks, significant differences vs placebo+low-dose metformin with dapagliflozin 5 and 10 mg were observed for HbA _{1c} (-5.8 mmol/mol [-0.53%], P=0.018; and -4.8 mmol/mol [-0.44%], P=0.048), respectively; and for FPG (-0.69 mmol/L, P=0.044; and -1.12 mmol/l, P=0.001, respectively). For body weight, the difference between the dapagliflozin 10-mg group and the placebo+low-dose metformin group was significant (-2.60 kg; P=0.016). Hypoglycemic events were uncommon, with rates of 5.3% for placebo+low-dose metformin group and 0 to 4.6% for the dapagliflozin groups. Genital infections and urinary tract infections were more common in the dapagliflozin groups than in the placebo+low-dose metformin group. The proportion of participants who achieved a level of HbA _{1c} <7% at 102 weeks was greater in the dapagliflozin 5 mg (33.2%) than in the placebo+low-dose metformin group (18.5%), resulting in a dapagliflozin 5 mg vs placebo+low-dose metformin group difference of 14.8% (95% CI, 0.3 to 29.2). Secondary: Not reported
Henry et al. ³²	AC, DB, MC, PG,	N=598 for	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2012)</p> <p>Dapagliflozin 5 or 10 mg QD</p> <p>vs</p> <p>metformin extended-release titrated to 2,000 mg daily</p> <p>vs</p> <p>dapagliflozin 5 or 10 mg QD and metformin titrated to 2,000 mg daily</p> <p>Dapagliflozin was dosed at 5 mg QD and 10 mg QD in the first and second trials, respectively.</p>	<p>RCT</p> <p>Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately controlled blood sugar, BMI ≤45 kg/m² and fasting C-peptide ≥0.34 ng/mL</p>	<p>Study 1, N=638 for Study 2</p> <p>2 trials each 24 weeks in duration</p>	<p>Change from baseline in HbA_{1c}</p> <p>Secondary: Change from baseline in FPG and body weight, glucose after two hour liquid meal, percentage of patients with HbA_{1c} <7.0% and safety assessments</p>	<p>Combination therapy led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin and metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001).</p> <p>In Study 2, treatment with dapagliflozin 10 mg (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.</p> <p>Secondary: Combination therapy was statistically superior to monotherapy in reduction of FPG (P<0.0001 for both studies); combination therapy was more effective than metformin for weight reduction (P<0.0001).</p> <p>Events suggestive of genital infection were reported in 6.7, 6.9 and 2.0% (Study 1) and 8.5, 12.8 and 2.4% (Study 2) of patients in combination, dapagliflozin and metformin groups; events suggestive of urinary tract infection were reported in 7.7, 7.9 and 7.5% (Study 1) and 7.6, 11.0 and 4.3% (Study 2) of patients in the respective groups.</p> <p>No major hypoglycemia was reported.</p>
<p>Roden et al.³³ (2013)</p> <p>Empagliflozin 10 mg QD</p> <p>vs</p> <p>empagliflozin 25 mg QD</p> <p>vs</p>	<p>AC, DB, MC, PC, RCT</p> <p>Patients with type 2 DM and HbA_{1c} of ≥7% to <10%</p>	<p>N=986</p> <p>24 weeks</p>	<p>Primary: HbA_{1c}</p> <p>Secondary: FPG, body weight, SBP and safety evaluations</p>	<p>Primary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} compared to placebo (-0.7% and -0.8% vs 0.1%, respectively; P<0.0001 for both comparisons).</p> <p>In the active comparator analysis, adjusted mean difference in change from baseline HbA_{1c} at week 24 was -0.73% (95% CI, -0.88 to -0.59; P<0.0001) for sitagliptin compared to placebo.</p> <p>Secondary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in FPG (-19 mg/dL and -25 mg/dL vs 12 mg/dL,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>sitagliptin 100 mg QD</p> <p>vs</p> <p>placebo</p>				<p>respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs -0.4 kg, respectively; P values not reported) compared with placebo.</p> <p>SBP was statistically significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -3.4 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin.</p> <p>There were 140 (61%) patients in the placebo group that reported adverse events (four [2%] severe and six [3%] serious), as did 123 (55%) patients in the empagliflozin 10 mg group (eight [4%] severe and eight [4%] serious), 135 (60%) patients in the empagliflozin 25 mg group (seven [3%] severe and five [2%] serious), and 119 (53%) patients in the sitagliptin group (five [2%] severe and six [3%] serious).</p>
<p>Barnett et al.³⁴ (2014)</p> <p>Empagliflozin 10 mg QD</p> <p>vs</p> <p>empagliflozin 25 mg QD</p> <p>vs</p> <p>placebo</p> <p>Patients with Stage III chronic kidney disease (eGFR \geq <60 mL/min/1.73 m²) were only assigned to the empagliflozin 25 mg QD arm.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with type 2 DM, HbA_{1c} of \geq7% to <10%, BMI \leq45 kg/m² and a baseline eGFR <90 mL/min/1.73 m²</p>	<p>N=738; 290 with mild renal impairment ([eGFR \geq60 to <90 mL/min/1.73 m²], 374 with moderate renal impairment [eGFR \geq30 to <60 mL/min/1.73 m²], and 74 with severe renal impairment [eGFR <30 mL/min/1.73 m²]).</p> <p>52 weeks</p>	<p>Primary: HbA_{1c}</p> <p>Secondary: FPG, body weight, SBP and safety evaluations</p>	<p>Primary:</p> <p>At week 24, empagliflozin 25 mg provided statistically significant reduction in HbA_{1c} relative to placebo in patients with mild to moderate renal impairment (-0.5% placebo-corrected comparison; P<0.0001). The glucose lowering efficacy decreased with decreasing level of renal function in the mild to moderate range. For patients with severe renal impairment, the analyses of changes in HbA_{1c} and FPG showed no discernible treatment effect compared to placebo.</p> <p>Secondary:</p> <p>At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG in the mild renal impairment group (-13.86 mg/dL and -18 mg/dL vs 5.58 mg/dL, respectively; P<0.0001) and moderate renal impairment group (-9 mg/dL vs 10.8 mg/dL, respectively; P<0.0001).</p> <p>Significant body weight and SBP decreases were noted in most treatment comparisons.</p> <p>Adverse events included UTI and genital mycotic infections.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Combination Therapy				
Rosenstock et al. ³⁵ (2012) Canagliflozin 50 mg QD vs canagliflozin 100 mg QD vs canagliflozin 200 mg QD vs canagliflozin 300 mg QD vs canagliflozin 300 mg BID vs sitagliptin 100 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with T2DM, an HbA _{1c} ≥7.0 and <10.5%, were on metformin monotherapy at a stable (≥3 months) dose of ≥1,500 mg/day, had a stable body weight and BMI 25 to 45 kg/m ² (24 to 45 kg/m ² for those of Asian descent), and had serum creatinine <1.5 mg/dL for men and <1.4 mg/dL for women	N=451 12 weeks	Primary: Change in HbA _{1c} level from baseline to week 12 Secondary: Change in FPG, change in body weight, and overnight urinary glucose -to-creatinine ratio	Primary: At 12 weeks, significant reductions in HbA _{1c} were observed in all canagliflozin treatment groups compared placebo (-0.79, -0.76, -0.70, -0.92, -0, and -0.95% for canagliflozin 50, 100, 200, and 300 mg QD and 300 mg BID, respectively, vs -0.22% for placebo; P<0.001 for all doses). At 12 weeks, significant reductions in HbA _{1c} were observed with sitagliptin 100 mg compared to placebo (-0.74 vs -0.22%; P<0.001). Secondary: At 12 weeks, a greater proportion of patients achieved the target HbA _{1c} <7.0% with canagliflozin doses of 100 mg QD and above (53 to 72%) and with sitagliptin (65%) compared to placebo (34%; P<0.05 for canagliflozin and sitagliptin). Significantly greater reductions in FPG were observed at 12 weeks with all canagliflozin doses (-16.2 to -27.0 mg/dL) compared to an increase observed with placebo (3.6 mg/dL; P<0.001 for all doses). FPG reductions were maximized with the 200 mg QD dose. Sitagliptin reduced FPG -12.6 mg/dL (P value compared to placebo not reported). Significant weight reductions were observed in canagliflozin groups relative to placebo, -2.3 to -3.4% (-2.0 to -2.9 kg; P<0.001 for all doses) at week 12. Reductions observed in the placebo and sitagliptin treatment groups were -1.1% (-0.8 kg) and -0.6% (-0.4 kg) from baseline, respectively. All doses of canagliflozin increased the overnight urinary glucose-to-urinary creatinine ratio (35.4 to 61.6 mg/mg) as compared to placebo (1.9 mg/mg; P<0.001 for all doses). Sitagliptin reduced urinary glucose-to-urinary creatinine ratio -1.9 mg/mg (P value compared to placebo not reported).
Lavalle-González et al. ³⁶	DB, PG, RCT	N=1,284	Primary: Change from	Primary: At week 26, canagliflozin 100 mg and 300 mg significantly reduced

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2013)</p> <p>canagliflozin 100 mg</p> <p>vs</p> <p>canagliflozin 300 mg</p> <p>vs</p> <p>sitagliptin 100 mg</p> <p>vs</p> <p>placebo</p>	<p>Patients with type 2 diabetes aged ≥ 18 and ≤ 80 years who had inadequate glycemic control ($HbA_{1c} \geq 7.0\%$ and $\leq 10.5\%$) on metformin therapy</p>	<p>2 week placebo run-in, 26 week placebo- and active-control treatment period (period I), followed by a 26 week active-control treatment period (period II), and a 4 week follow-up period</p>	<p>baseline in HbA_{1c} at week 26</p> <p>Secondary: Changes in HbA_{1c} (week 52) and FPG, body weight, and systolic blood pressure (BP; weeks 26 and 52), adverse events</p>	<p>HbA_{1c} from baseline compared with placebo ($P < 0.001$ for both).</p> <p>Secondary: At week 26, a greater proportion of participants treated with canagliflozin 100 mg and 300 mg achieved $HbA_{1c} < 7.0\%$ than with placebo (45.5, 57.8, and 29.8%, respectively; $P = 0.000$ for both); 54.5% of sitagliptin-treated participants achieved $HbA_{1c} < 7.0\%$. Both canagliflozin doses significantly reduced FPG and 2-hour PPG at week 26 vs placebo ($P < 0.001$ for all); FPG and 2-hour PPG were also reduced from baseline with sitagliptin.</p> <p>At 52 weeks, canagliflozin 100 mg and 300 mg demonstrated non-inferiority to sitagliptin 100 mg in HbA_{1c}-lowering effect. Canagliflozin 300 mg demonstrated statistical superiority to sitagliptin in HbA_{1c}-lowering effect. Canagliflozin 100 mg and 300 mg significantly reduced body weight compared with sitagliptin. Canagliflozin 100 mg and 300 mg significantly decreased systolic BP relative to sitagliptin at 52 weeks. The change in diastolic BP from baseline was -1.8 mmHg with both canagliflozin doses and -0.3 mmHg with sitagliptin.</p> <p>Overall incidences of adverse events and adverse event-related discontinuations were generally comparable across groups over 52 weeks. Canagliflozin was associated with a higher incidence of genital mycotic infections in men and women. These were generally mild or moderate in intensity and led to few discontinuations.</p>
<p>Neal et al.³⁷ (2015) CANVAS</p> <p>Canagliflozin 100 mg</p> <p>vs</p> <p>canagliflozin 300 mg</p> <p>vs</p>	<p>DB, MC, PC, RCT</p> <p>Patients with type 2 diabetes who have inadequate glycemic control ($HbA_{1c} \geq 7.0\%$ and $\leq 10.5\%$), despite current management with glucose-lowering strategies, and are at an elevated risk of</p>	<p>N=2,074</p> <p>52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline at week 18</p> <p>Secondary: Body weight, FPG, blood pressure, lipids at 18 and 52 weeks</p>	<p>Primary: Both doses of canagliflozin significantly reduced the primary outcome of HbA_{1c} relative to placebo at week 18 (both $P < 0.001$), with comparable reductions also seen at week 52.</p> <p>Secondary: There were also reductions in the secondary outcomes of body weight and FPG (all $P < 0.001$) and increases in the proportion of patients achieving $HbA_{1c} < 7.0\%$ (both $P < 0.001$) with both canagliflozin doses versus placebo at week 18. Similar effects were seen for all outcomes at week 52. Canagliflozin 100 and 300 mg also provided dose-dependent reductions in systolic blood pressure compared with placebo at both time points. The higher dose of canagliflozin raised HDL cholesterol levels compared with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo</p> <p>used in addition to insulin therapy at a dose of ≥ 20 IU/day</p>	<p>cardiovascular disease</p>			<p>placebo at both 18 and 52 weeks, but the lower dose raised levels only at 52 weeks. Canagliflozin 100 and 300 mg caused an elevation in LDL cholesterol at 18 and 52 weeks, but there was no detectable change in the ratio of LDL cholesterol to HDL cholesterol at either time point for either dose.</p>
<p>Cefalu et al.³⁸ CANTATA-SU (2013)</p> <p>Canagliflozin 100 mg</p> <p>vs</p> <p>canagliflozin 300 mg</p> <p>vs</p> <p>glimepiride titrated to a maximum of 6 or 8 mg/day</p>	<p>AC, DB, NI, RCT</p> <p>Patients aged 18 to 80 years with type 2 diabetes and an HbA_{1c} between 7.0 and 9.5% receiving stable metformin therapy</p>	<p>N=1,450</p> <p>52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Percentage change from baseline in bodyweight, proportion of patients with documented hypoglycemic episodes</p>	<p>Primary: Both canagliflozin doses were non-inferior to glimepiride for lowering of HbA_{1c}, and canagliflozin 300 mg was superior to glimepiride for HbA_{1c} reduction. The least squares mean change from baseline was -0.81, -0.82, and -0.93% in the glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.</p> <p>Secondary: The proportion of patients with documented hypoglycemic episodes was significantly lower with canagliflozin 100 mg and 300 mg than with glimepiride (P<0.0001 for both). The frequency of severe hypoglycemia was also lower with canagliflozin 100 mg (two [$<1\%$] patients) and 300 mg (three [$<1\%$]) than with glimepiride (15 [3%]).</p> <p>Both canagliflozin doses significantly reduced bodyweight at week 52, whereas a slight increase occurred with glimepiride (P<0.0001 for both canagliflozin doses vs glimepiride).</p>
<p>Leiter et al.³⁹ (2015)</p> <p>Canagliflozin 100 mg</p> <p>vs</p> <p>canagliflozin 300 mg</p> <p>vs</p> <p>glimepiride</p>	<p>DB, MC, RCT</p> <p>Patients ≥ 18 and ≤ 80 years of age with type 2 diabetes and HbA_{1c} $\geq 7.0\%$ and $\leq 9.5\%$ whose conditions were stable while receiving metformin therapy ($\geq 2,000$ mg/day, or $\geq 1,500$ mg/day if unable to tolerate a higher</p>	<p>N=1,450</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 52</p> <p>Secondary: Change in HbA_{1c}, FPG, blood pressure, body weight, and lipids at week 104</p>	<p>Primary: Both canagliflozin doses were non-inferior to glimepiride for lowering of HbA_{1c}, and canagliflozin 300 mg was superior to glimepiride for HbA_{1c} reduction.</p> <p>Secondary: Over 104 weeks, canagliflozin 100 and 300 mg and glimepiride reduced HbA_{1c} from mean baseline values of 7.78, 7.79, and 7.83% (62 mmol/mol for all), respectively, with changes from baseline to week 104 of -0.65, -0.74, and -0.55% (-7.1, -8.1, and -6.0 mmol/mol), respectively. Reductions in body weight (-4.1, -4.2, and 0.9%, respectively) and systolic blood pressure (-2.0, -3.1, and 1.7 mmHg, respectively) were seen with canagliflozin 100 and 300 mg compared with glimepiride at week 104.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(titrated up to 6 or 8 mg/day)	dose) for ≥10 weeks			The overall adverse event incidence was 73.3, 77.9, and 78.4% with canagliflozin 100 and 300 mg and glimepiride; the incidence of adverse event-related discontinuations was low across groups (6.2, 9.5, and 7.3%, respectively). Incidences of genital mycotic infections, urinary tract infections, and osmotic diuresis–related adverse events were higher with canagliflozin than glimepiride; these were generally mild to moderate in intensity and led to few discontinuations. Fewer patients had hypoglycemia episodes with canagliflozin 100 and 300 mg than glimepiride (6.8, 8.2, and 40.9%). Mild decreases in estimated glomerular filtration rate occurred initially with canagliflozin; these attenuated over 104 weeks.
<p>Rosenstock et al.⁴⁰ (2016)</p> <p>Canagliflozin 100 mg and metformin XR</p> <p>vs</p> <p>Canagliflozin 300 mg and metformin XR</p> <p>vs</p> <p>Canagliflozin 100 mg</p> <p>vs</p> <p>Canagliflozin 300 mg</p>	<p>DB, RCT</p> <p>Patients with drug-naïve type 2 diabetes from 18 to 75 years of age</p>	<p>N=1,186</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Noninferiority in HbA_{1c} lowering with canagliflozin monotherapy versus metformin; changes in FPG, body weight, and SBP; and proportion of patients achieving HbA_{1c} <7.0%</p>	<p>Primary: At week 26, reductions from baseline in HbA_{1c} were seen with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET (–1.77, –1.78, –1.37, –1.42, and –1.30%, respectively), resulting in final mean HbA_{1c} values of 7.0, 7.0, 7.4, 7.3, and 7.4%, respectively. Reductions in HbA_{1c} with CANA100/MET and CANA300/MET were statistically significant versus MET (LS mean differences of –0.46% and –0.48%, respectively; P=0.001 for both) and versus CANA100 and CANA300 (LS mean differences of –0.40% and –0.36%, respectively; P=0.001 for both).</p> <p>Secondary: Noninferiority of HbA_{1c} lowering was also demonstrated with CANA100 and CANA300 versus MET (LS mean differences of –0.06% and –0.11%, respectively; noninferiority P=0.001 for both). At week 26, significant differences in the proportion of patients who achieved HbA_{1c} <7.0% were observed with CANA100/MET and CANA300/MET versus MET (P=0.027 and P=0.016, respectively); 49.6%, 56.8%, 38.8%, 42.8%, and 43.0% of patients achieved HbA_{1c} <7.0% with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively.</p> <p>Dose-related reductions in FPG were observed with CANA100/MET and CANA300/MET that were greater compared with their respective monotherapies. At week 26, reductions in body weight from baseline were observed across groups (–3.2, –3.9, –2.8, –3.7, and –1.9 kg [–3.5%, –</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin XR (Metformin XR doses were titrated)				4.2%, -3.0%, -3.9%, and -2.1%] with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively). CANA100/MET, CANA300/MET, CANA100, and CANA300 provided modest reductions in SBP compared with MET (-2.2, -1.7, -2.2, -2.4, and -0.3 mmHg, respectively). Reductions in SBP with CANA100/MET and CANA300/MET were not statistically significant versus MET (LS mean differences of -1.9 and -1.3 mmHg, respectively).
Nauck et al. ⁴¹ (2011) Dapagliflozin 10 mg QD vs glipizide 10 mg BID Studied agent added on to OL dosed metformin.	AC, DB, MC, PG, RCT Patients with T2DM, ≥18 years of age, who were previously treated with oral anti-diabetic agents, inadequately controlled blood sugar, BMI ≤45 kg/m ² and fasting C-peptide ≥0.34 ng/mL	N=801 52 weeks	Primary: Change from baseline in HbA _{1c} Secondary: Change from baseline in body weight, percentage of patients who lost >5% of body weight, percentage of patients with ≥1 hypoglycemic event and systolic blood pressure changes	Primary: At week 52, both dapagliflozin plus metformin and glipizide plus metformin therapies had identical HbA _{1c} reductions of 0.52% which met the criteria for non-inferiority. Secondary: Treatment with dapagliflozin resulted in weight loss of -3.22 kg vs weight gain of 1.44 kg with glipizide. Other secondary endpoints including percentage of patients who lost >5% of body weight and percentage of patients with ≥1 hypoglycemic event also favored dapagliflozin (P<0.001). Mean systolic blood pressure was reduced with dapagliflozin but not with glipizide at 208 weeks (in an extension cohort): difference, -3.67 mmHg (95% CI, -5.92 to -1.41).
Del Prato et al. ⁴² (2015) Dapagliflozin vs glipizide Studied agent added on to OL dosed metformin.	DB, MC, RCT Patients with T2DM, ≥18 years of age, who were previously treated with oral anti-diabetic agents, inadequately controlled blood sugar, BMI ≤45 kg/m ² and fasting C-peptide ≥0.34 ng/mL	N=801 4 year extension study	Primary: Therapeutic glycaemic response defined as HbA _{1c} <7.0% Secondary: FPG, blood pressure, body weight, safety	Primary: At 208 weeks, dapagliflozin compared with glipizide produced sustained reductions in HbA _{1c} : -0.30% (95% CI, -0.51 to -0.09), in total body weight: -4.38 kg (95% CI -5.31 to -3.46) and in systolic blood pressure: -3.67 mmHg (95% CI -5.92 to -1.41). Secondary: Dapagliflozin was not associated with glomerular function deterioration, while this occurred more frequently in patients in the glipizide group. Fewer patients reported hypoglycaemia in the dapagliflozin compared with the glipizide group (5.4 vs 51.5%). Genital and urinary tract infections were more common with dapagliflozin than with glipizide, but their incidence decreased with time and all events responded well to antimicrobial treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Bailey et al.⁴³ (2010)</p> <p>Dapagliflozin 2.5 mg QD</p> <p>vs</p> <p>dapagliflozin 5 mg QD</p> <p>vs</p> <p>dapagliflozin 10 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 77 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% who have been on a stable dose of metformin ($\geq 1,500$ mg/day) for ≥ 8 weeks</p>	<p>N=546</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline at week 24</p> <p>Secondary: Change in fasting blood glucose and weight from baseline at week 24</p>	<p>Primary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in a significantly greater reduction from baseline to week 24 in HbA_{1c} compared to placebo plus metformin (-0.67, -0.70 and -0.84 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.30 for placebo; P<0.05 for all).</p> <p>Secondary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose and weight compared to the placebo group (P<0.05 for all).</p>
<p>Bailey et al.⁴⁴ (2013)</p> <p>Dapagliflozin 2.5 mg QD</p> <p>vs</p> <p>dapagliflozin 5 mg QD</p> <p>vs</p> <p>dapagliflozin 10 mg QD</p> <p>vs</p>	<p>DB, ES, MC, PC, PG, RCT</p> <p>Patients 18 to 77 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% who have been on a stable dose of metformin ($\geq 1,500$ mg/day) for ≥ 8 weeks</p>	<p>N=546</p> <p>102 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline at week 102</p> <p>Secondary: Change in fasting blood glucose and weight from baseline at week 102</p>	<p>Primary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in significantly greater reductions from baseline to week 102 in HbA_{1c} compared to placebo (-0.48, -0.58 and -0.78 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to 0.02 for placebo; P=0.008 for dapagliflozin 2.5 mg vs placebo and P<0.0001 for dapagliflozin 5 and 10 mg vs placebo).</p> <p>Secondary: Patients treated with all doses of dapagliflozin achieved sustained reductions in fasting blood glucose (-1.07 to -1.47) and weight (-1.10 to -1.74) at week 102 compared to increases in fasting blood glucose and weight in the placebo group.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Bolinder et al. ⁴⁵ (2012) Dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Diabetic patients	N=182 24 weeks	Primary: Change in total body weight from baseline at week 24 Secondary: Change in waist circumference and dual-energy x-ray absorptiometry total-body fat mass from baseline at week 24, proportion of patients achieving body weight reduction of $\geq 5\%$ at week 24	Primary: Treatment with dapagliflozin plus metformin resulted in a placebo-corrected reduction in total body weight of -2.08 kg at week 24 (95% CI, -2.84 to -1.31; P<0.0001). Secondary: Treatment with dapagliflozin plus metformin resulted in placebo-corrected reductions in waist circumference and dual-energy x-ray absorptiometry total-body fat mass of -1.52 cm (95% CI, -2.74 to -0.31; P=0.0143) and -1.48 kg (95% CI, -2.22 to -0.74; P=0.0001), respectively, at week 24. The placebo-corrected proportion of patients treated with dapagliflozin plus metformin who achieved $\geq 5\%$ weight reduction was 26.2% (95% CI, 15.5 to 36.7; P<0.0001).
Strojek et al. ⁴⁶ (2011) Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs	DB, MC, PC, PG, RCT Patients ≥ 18 years of age with T2DM with a HbA _{1c} of 7.0 to 10.0% and a fasting blood glucose ≤ 15 mmol/L who were stabilized on a sulfonylurea monotherapy dose at least half the maximal recommended dose for ≥ 8 weeks	N=596 24 weeks	Primary: Change in HbA _{1c} from baseline at week 24 Secondary: Change in fasting blood glucose and weight from baseline at week 24	Primary: Compared to placebo plus glimepiride, treatment with dapagliflozin in combination with glimepiride resulted in a significantly greater reduction in HbA _{1c} from baseline to week 24 across all dapagliflozin treatment arms (-0.58, -0.63 and -0.82 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.13 for placebo; P<0.0001 for all). Secondary: Compared to placebo plus glimepiride, treatment with dapagliflozin 5 and 10 mg in combination with glimepiride resulted in a significantly greater reduction in fasting blood glucose from baseline to week 24 (-1.18 and -1.58 for dapagliflozin 5 and 10 mg, respectively, compared to -0.11 for placebo; P<0.0001 for both). Treatment with dapagliflozin 2.5 mg plus glimepiride did not result in a significantly greater reduction in fasting blood glucose compared to placebo plus glimepiride. Patients treated with dapagliflozin 5 or 10 mg plus glimepiride achieved

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				significantly greater reductions in weight from baseline to week 24 compared to placebo plus glimepiride (-1.56 and -2.26 for dapagliflozin 5 and 10 mg, respectively, compared to -0.72 for placebo; P<0.01 and P<0.0001, respectively). Treatment with dapagliflozin 2.5 mg plus glimepiride did not result in a significantly greater reduction in weight compared to placebo plus glimepiride.
Rosenstock et al. ⁴⁷ (2012) Dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with T2DM with a HbA _{1c} of 7.0 to 10.5% who were treatment naïve or who had previously received metformin, a sulfonylurea or pioglitazone	N=420 24 weeks plus 24-week extension trial	Primary: Change in HbA _{1c} from baseline at week 24 Secondary: Change from baseline at week 24 in FPG, two-hour PPG and weight	Primary: Treatment with dapagliflozin plus pioglitazone resulted in significantly greater reductions in HbA _{1c} from baseline to week 24 compared to placebo plus pioglitazone (-0.82 and -0.97 for dapagliflozin 5 mg and 10 mg, respectively; P=0.0007 and P<0.0001, respectively). Secondary: Treatment with dapagliflozin 5 or 10 mg plus pioglitazone resulted in significantly greater reductions in FPG, two hour PPG and weight from baseline to week 24 (P<0.0001 for all).
Schernthaner et al. ⁴⁸ (2013) (abstract) Canagliflozin 300 mg QD vs sitagliptin 100 mg QD vs placebo	AC, DB, RCT Patients with T2DM, receiving a stable dose of metformin and a sulfonylurea	N=755 52 weeks	Primary: Change in HbA _{1c} level from baseline to week 52 Secondary: Change in FPG, systolic blood pressure, body weight, triglycerides, and HDL-C	Primary: At the end of the 52 treatment period, canagliflozin 300 mg once daily was considered non-inferior to and produced significant reductions in HbA _{1c} compared to sitagliptin 100 mg QD (-1.03 and -0.66%; difference, 0.37%; 95% CI, -0.50 to -0.25). Secondary: At week 52, greater reductions in FPG, body weight, and systolic blood pressure were observed with canagliflozin vs sitagliptin (P<0.001).
Jabbour et al. ⁴⁹	DB, MC, PC, PG,	N=432	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2014)</p> <p>Dapagliflozin 10 mg QD ± metformin</p> <p>vs</p> <p>placebo ± metformin</p> <p>Patients taking metformin received doses ≥1,500 mg/day.</p>	<p>RCT</p> <p>Patients aged ≥18 years with T2DM with a HbA_{1c} of 7.0 to 10.5% who were treatment naïve or who had previously received metformin, sitagliptin, vitagliptin or a combination</p>	<p>24 weeks</p>	<p>Change in HbA_{1c} from baseline at week 24</p> <p>Secondary: Change from baseline at week 24 in fasting blood glucose, two-hour PPG and weight</p>	<p>Treatment with dapagliflozin plus sitagliptin resulted in a significantly greater reduction in HbA_{1c} from baseline to week 24 compared to placebo plus sitagliptin (-0.5 vs 0.1; P<0.0001). Similarly, treatment with dapagliflozin, sitagliptin and metformin combination therapy resulted in a significantly greater reduction in HbA_{1c} compared to the placebo, sitagliptin and metformin group (-0.4 vs -0.0; P<0.0001).</p> <p>Secondary: Treatment with dapagliflozin plus sitagliptin and dapagliflozin, sitagliptin and metformin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose, two hour PPG and weight compared to their respectively placebo comparator groups (P<0.0001 for all).</p>
<p>Cefalu et al.⁵⁰ (2015)</p> <p>Dapagliflozin 10 mg QD</p> <p>vs</p> <p>placebo</p> <p>plus pre-existing stable background treatment, excluding rosiglitazone</p>	<p>DB, MC, PC, RCT</p> <p>Patients with type 2 diabetes, documented pre-existing cardiovascular disease, and a history of hypertension</p>	<p>N=922</p> <p>24 weeks plus 28-week extension trial</p>	<p>Primary: Change in HbA_{1c} from baseline and the proportion of patients achieving a combined reduction in HbA_{1c} of ≥0.5%, body weight of ≥3%, and SBP of ≥3 mmHg</p> <p>Secondary: Blood pressure, body weight, FPG, safety</p>	<p>Primary: At 24 weeks, dapagliflozin significantly reduced HbA_{1c} (-0.38%) from baseline compared with a slight increase with placebo from baseline (0.08%). Significantly more patients met the three-item end point with treatment with dapagliflozin than with placebo (11.7 vs 0.9%, respectively). Changes were maintained over 52 weeks.</p> <p>Secondary: Greater reductions in mean seated SBP from baseline were observed at week 24 after treatment with dapagliflozin than with placebo. The mean placebo-subtracted seated reduction in SBP was statistically significant at week 8 (-1.97 mmHg), and was maintained at week 24 (-1.95 mmHg) and week 52 (-3.58 mmHg) (P<0.0001). A greater reduction in mean body weight was observed in patients treated with dapagliflozin versus placebo at week 24 (-2.56 vs -0.30%) and was maintained through week 52 (-2.89 vs -0.29%). The placebo-corrected reduction in body weight was significant at week 24 (-2.10 kg, nominal P<0.05) and persisted through week 52 (-2.51 kg). Patients in the dapagliflozin group, excluding those who received rescue therapy, showed a rapid mean reduction in FPG from baseline at week one that was greater than that with placebo and was maintained through week 24 (-0.57 vs 0.35 mmol/L) and 52 weeks (-0.96 vs -0.01 mmol/L).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Rosenstock et al.⁵¹ (2015)</p> <p>Saxagliptin (SAXA) (5 mg/day) plus dapagliflozin (DAPA) (10 mg/day)</p> <p>vs</p> <p>SAXA (5 mg/day) and placebo</p> <p>vs</p> <p>DAPA (10 mg/day) and placebo</p>	<p>DB, RCT</p> <p>Type 2 diabetics with HbA_{1c} ≥8.0% and ≤12.0% on background metformin extended release ≥1,500 mg/day</p>	<p>N=534</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Adjusted mean change from baseline in 2-h PPG, FPG, and body weight, adjusted mean proportion of patients achieving a therapeutic glycemic response, defined as HbA_{1c} <7.0%</p>	<p>Primary: At week 24, the adjusted mean change from the baseline HbA_{1c} was -1.5% with SAXA+DAPA+MET vs -0.9% with SAXA+MET (difference -0.59%, P<0.0001) and -1.2% with DAPA+MET (difference -0.27%, P<0.02).</p> <p>Secondary: The adjusted mean reduction in FPG was greater in the SAXA+DAPA+MET group (-38 ± 2.8 mg/dL) than in the SAXA+MET group (-14 ± 2.9 mg/dL) but similar to the DAPA+MET group (-32 ± 2.8 mg/dL). SAXA+DAPA+MET also resulted in a significantly greater adjusted mean reduction from baseline in PPG versus SAXA+MET (difference, -44 mg/dL; 95% CI, -53.7 to -34.3; P<0.0001) but not versus DAPA+MET (difference, -9 mg/dL; 95% CI, -18.8 to 0.5; P=0.06). Reduction in body weight of 2.1 kg (2.4%) was observed in the SAXA+DAPA+MET group and 2.4 kg (2.8%) in the DAPA+MET group compared with no change in the SAXA+MET group. The proportion of patients achieving HbA_{1c} <7% was 41% with SAXA+DAPA+MET versus 18% with SAXA+MET and 22% with DAPA+MET. Urinary and genital infections occurred in ≤1% of patients receiving SAXA+DAPA+MET. Hypoglycemia was infrequent, with no episodes of major hypoglycemia.</p>
<p>Wilding et al.⁵² (2012)</p> <p>Dapagliflozin 2.5 mg QD ± oral antidiabetic agent</p> <p>vs</p> <p>dapagliflozin 5 mg QD ± oral antidiabetic agent</p> <p>vs</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 80 years of age with T2DM, BMI ≤45 kg/m² and a HbA_{1c} of 7.5 to 10.5% who are stabilized on an insulin regimen of >30 IU/day for ≥8 weeks ± other oral antidiabetic agents</p>	<p>N=800</p> <p>24 weeks plus 24-week extension trial</p>	<p>Primary: Change in HbA_{1c} from baseline at week 24</p> <p>Secondary: Change from baseline to week 24 in fasting blood glucose, insulin dose and weight</p>	<p>Primary: Treatment with dapagliflozin plus insulin resulted in a significant decrease from baseline to week 24 in HbA_{1c} across all doses compared to placebo plus insulin (-0.79, -0.89 and -0.96 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.39 for placebo; P<0.001 for all).</p> <p>Secondary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus insulin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose, insulin dose and weight compared to placebo (P<0.001 for all).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dapagliflozin 10 mg QD ± oral antidiabetic agent vs placebo				
Häring et al. ⁵³ (2014) Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with metformin.	DB, MC, PC, RCT Patients with type 2 DM and HbA _{1c} of ≥7% to <10%, inadequately controlled on ≥ 1,500 mg of metformin per day	N=637 24 weeks	Primary: HbA _{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA _{1c} compared to placebo (-0.7% and -0.8% vs 0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-20 mg/dL and -22 mg/dL vs 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo. SBP was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -4.8 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. Confirmed hypoglycemic adverse events were reported in 0.5%, 1.8%, and 1.4% of patients receiving placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Events consistent with urinary tract infections were reported in 4.9%, 5.1%, and 5.6% of patients, and events consistent with genital infections were reported in 0%, 3.7%, and 4.7% of patients, respectively.
Ridderstråle et al. ⁵⁴ (2014) Empagliflozin 25 mg QD vs	AC, DB, MC, RCT Patients with type 2 DM and HbA _{1c} of ≥7% to <10%, inadequately controlled on	N=1,545 104 weeks	Primary: HbA _{1c} (tested for non-inferiority at week 52, tested for superiority at week 104)	Primary: At week 52, empagliflozin 25 mg meet the non-inferiority criteria for lowering HbA _{1c} compared to glimepiride (-0.7% vs -0.7%). Non-inferiority continued to be demonstrated at week 104. In addition, at week 104, adjusted mean difference in change from baseline in HbA _{1c} with empagliflozin versus glimepiride was -0.11%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>glimepiride 1 to 4 mg QD</p> <p>Patients continued treatment with metformin.</p>	<p>metformin monotherapy</p>		<p>Secondary: FPG, body weight, SBP and safety evaluations</p>	<p>(95% CI, -0.19 to -0.02; P=0.0153 for superiority).</p> <p>Secondary: At week 52, There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride; however, the significance was not reported (-19 mg/dL vs -9 mg/dL and -3.9 kg vs 2 kg; P values not reported).</p> <p>SBP was also statistically significantly reduced compared to glimepiride (-3.6 mmHg vs 2.2 mmHg; P<0.0001).</p> <p>Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3.9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with empagliflozin and 189 (24%) patients treated with glimepiride.</p>
<p>Häring et al.⁵⁵ (2013)</p> <p>Empagliflozin 10 mg QD</p> <p>vs</p> <p>empagliflozin 25 mg QD</p> <p>vs</p> <p>placebo</p> <p>Patients continued treatment with</p>	<p>DB, MC, PC, RCT</p> <p>Patients aged ≥18 years with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on ≥1,500 mg of metformin per day and a sulfonylurea</p>	<p>N=666</p> <p>24 weeks</p>	<p>Primary: HbA_{1c}</p> <p>Secondary: FPG, body weight, SBP and safety evaluations</p>	<p>Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.8% and -0.8% vs -0.2%, respectively; P<0.0001 for both comparisons).</p> <p>Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-23 mg/dL and -23 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.9 kg and -3.2 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo.</p> <p>Decreases in SBP were also significantly greater with both empagliflozin doses than placebo.</p> <p>Adverse events were reported in 62.7, 67.9, and 64.1% of patients on placebo and empagliflozin 10 and 25 mg, respectively. Events consistent</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin and sulfonylurea.				with urinary tract infection were reported in 8.0, 10.3, and 8.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 13.3, 18.0, and 17.5%, respectively; males: 2.7, 2.7, and 0%, respectively). Events consistent with genital infection were reported in 0.9, 2.7, and 2.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 0.9, 4.5, and 3.9%, respectively; males: 0.9% in each group).
Kovacs et al. ⁵⁶ (2014) Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with pioglitazone with or without metformin.	DB, MC, PC, RCT Patients with type 2 DM and HbA _{1c} of ≥7% to <10%, inadequately controlled on pioglitazone 30 mg per day, with or without metformin ≥1,500 mg per day	N=498 24 weeks	Primary: HbA _{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA _{1c} compared to placebo (-0.6% and -0.7% vs -0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-17 mg/dL and -22 mg/dL vs 7 mg/dL, respectively; P<0.001) and body weight (-2.0 kg and -1.8 kg vs -0.6 kg, respectively; P<0.001) compared with placebo. Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3.9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with empagliflozin and 189 (24%) patients treated with glimepiride. Similar proportions of patients reported adverse events with empagliflozin (67.3 to 71.4%) and placebo (72.7%). Confirmed hypoglycemia was reported by 1.2 to 2.4% of patients on empagliflozin and 1.8% on placebo.
Rosenstock et al. ⁵⁷ (2015) Empagliflozin 10 mg QD vs	DB, MC, PC, RCT Patients with type 2 diabetes and HbA _{1c} of ≥7% to <10%, inadequately controlled on basal insulin	N=494 78 weeks	Primary: Change in HbA _{1c} at week 18 Secondary: Change in HbA _{1c} and insulin dose at week 78	Primary: At week 18, adjusted mean ± standard error changes from baseline in HbA _{1c} were 0 ± 0.1% with placebo compared with -0.6 ± 0.1% with empagliflozin 10 mg and -0.7 ± 0.1% with empagliflozin 25 mg (both P<0.001). Secondary: At week 78, adjusted mean HbA _{1c} changes from baseline were 0 ± 0.1%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>empagliflozin 25 mg QD</p> <p>vs</p> <p>placebo</p> <p>as add-on to basal insulin, with or without metformin and/or sulphonylureas</p>				<p>with placebo compared with $-0.5 \pm 0.1\%$) with empagliflozin 10 mg and $-0.6 \pm 0.1\%$ with empagliflozin 25 mg (both $p < 0.001$). Adjusted mean changes from baseline in insulin doses were 5.5 ± 1.6 IU with placebo compared with -1.2 ± 1.5 IU with empagliflozin 10 mg ($P=0.002$) and -0.5 ± 1.6 IU with empagliflozin 25 mg ($P=0.009$).</p>
<p>Zinman et al.⁵⁸ (2015)</p> <p>EMPA-REG OUTCOME</p> <p>Empagliflozin 10 mg QD</p> <p>vs</p> <p>empagliflozin 25 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care</p>	<p>N=7,020</p> <p>Median observation time of 3.1 years</p>	<p>Primary: Composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke</p> <p>Secondary: Composite of the primary outcome plus hospitalization for unstable angina</p>	<p>Primary: The primary outcome occurred in a significantly lower percentage of patients in the empagliflozin group (490 of 4687 [10.5%]) than in the placebo group (282 of 2333 [12.1%]) (HR in the empagliflozin group, 0.86; 95.02% CI, 0.74 to 0.99; $P<0.001$ for noninferiority and $P=0.04$ for superiority).</p> <p>Secondary: The secondary outcome occurred in 599 of 4687 patients (12.8%) in the empagliflozin group and 333 of 2333 patients (14.3%) in the placebo group (HR, 0.89; 95% CI, 0.78 to 1.01; $P<0.001$ for noninferiority and $P=0.08$ for superiority).</p>
<p>Mearns et al.⁵⁹ (2015)</p> <p>Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4</p>	<p>Network MA (62 RCTs)</p> <p>Patients with inadequately controlled type 2 diabetes on metformin alone</p>	<p>N=32,185</p> <p>3 to 12 months</p>	<p>Primary: Changes in HbA_{1c}, body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection</p>	<p>Primary: All agents significantly reduced HbA_{1c} vs placebo; although not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulphonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulphonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)			Secondary: Not reported	SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported

Drug regimen abbreviations: BID=two times a day, QAM=once every morning, QD=once-daily, QPM=once every evening

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, OL=open label, MC=multicenter, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial

Miscellaneous: BMI=body mass index, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C= high density lipoprotein cholesterol, PPG=postprandial glucose, T2DM=type 2 diabetes mellitus

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 11. Relative Cost of the Sodium-glucose Cotransport 2 Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Canagliflozin	tablet	Invokana®	\$\$\$\$\$	N/A
Dapagliflozin	tablet	Farxiga®	\$\$\$\$\$	N/A
Empagliflozin	tablet	Jardiance®	\$\$\$\$\$	N/A
Combination Products				
Canagliflozin and Metformin	extended-release tablet, tablet	Invokamet®, Invokamet XR®	\$\$\$\$\$	N/A
Dapagliflozin and Metformin	extended-release tablet	Xigduo XR®	\$\$\$\$\$	N/A
Empagliflozin and Linagliptin	tablet	Glyxambi®	\$\$\$\$\$	N/A
Empagliflozin and Metformin	tablet	Synjardy®	\$\$\$\$\$	N/A

N/A=Not available

X. Conclusions

The sodium-glucose cotransport 2 (SGLT2) inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.³⁻¹³ Empagliflozin is also indicated to reduce the

risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.⁷ There are currently no generic products available.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin (HbA_{1c}) will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.¹⁴⁻²⁶ SGLT2 inhibitors are recommended as a potential first, second, or third-line treatment option to be added as an alternative to or in combination with metformin in patients not achieving glycemic goals. SGLT2 inhibitors are acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia.¹⁴⁻²⁶

and the SGLT2 inhibitors have demonstrated to be significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose.²⁷⁻³⁰ Combination and add-on therapy with SGLT2 inhibitors and metformin, a sulfonylurea, a thiazolidinedione, and insulin consistently demonstrates improved benefits in glycemic control over placebo. Currently no head-to-head trials comparing agents within the class been published.²⁷⁻⁵⁹ Limited trials have compared the SGLT2 inhibitors to other classes or oral antidiabetic agents: Studies thus far have demonstrated noninferiority to glimepiride, glipizide, and sitagliptin.^{38,39,41,48,54}

The EMPA-REG OUTCOME trial showed that empagliflozin therapy reduced the aggregate outcome of myocardial infarction, stroke, and cardiovascular death by 14% (absolute rate 10.5 vs 12.1% in the placebo group; P<0.001 for noninferiority and P=0.04 for superiority), due to a 38% reduction in cardiovascular death (absolute rate 3.7 vs 5.9%).⁵⁸ The American Diabetes Association Standards of Care in Diabetes state that empagliflozin is the first of the recently approved diabetes treatments associated with a lower risk of cardiovascular disease; however, whether empagliflozin or other SGLT2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.¹⁴

Though clinical experience is limited, the SGLT2 inhibitors are associated with several favorable side effects compared to other antidiabetic agents such as weight loss. Compared to sulfonylureas, the risk of hypoglycemia associated with the SGLT2 inhibitors is low as it reduces plasma glucose concentrations without stimulating insulin release or inhibiting its counterregulatory response.¹⁻⁴ During clinical trials, common adverse side effects associated with the SGLT2 inhibitors included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.³⁻¹²

There is insufficient evidence to support that one brand SGLT2 inhibitor is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand sodium-glucose cotransport 2 inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Abdul-Ghani MA, Norton L, DeFronzo RA. Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes mellitus. *Curr Diab Rep.* 2012 Jun;12(3):230-8.
2. Abdul-Ghani MA, Norton L, DeFronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr Rev.* 2011 Aug;32(4):515-31.
3. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Feb]. Available from: <http://www.thomsonhc.com/>.
4. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Feb 2017]. Available from: <http://online.factsandcomparisons.com>.
5. Invokana® [package insert]. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2017 Feb.
6. Farxiga® [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals; 2016 Aug.
7. Jardiance® [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2016 Dec.
8. Invokamet™ [package insert]. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2017 Feb.
9. Invokamet XR® [package insert]. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2016 Sep.
10. Xigduo XR® [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals; 2016 Aug.
11. Glyxambi® [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2016 Dec.
12. Synjardy® [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2016 Dec.
13. FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes [press release on the Internet]. Rockville (MD): Food and Drug Administration (US); 2016 Dec 2 [cited 2017 Feb 28]. Available from: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm531517.htm>.
14. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* 2016;39(Suppl. 1):S1–S112.
15. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012 Jun;35(6):1364-79.
16. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia.* 2015 Mar;58(3):429-42.
17. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2012 Feb 7;156(3):218-31.
18. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract.* 2015 Apr;21 Suppl 1:1-87.
19. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. *Endocr Pract.* 2016;22(1):84-113.
20. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
21. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
22. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
23. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. *Pediatrics* 2013;131(2):364-382.
24. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.
25. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.

26. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. *Diabetes Care* 2014;37(7):2034-2054.
27. Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. Published online January 24, 2013. doi: 10.1111/dom.12054.
28. Bode B, Stenlof K, Sullivan D, et al. Efficacy and safety of canagliflozin, a sodium glucose cotransporter 2 inhibitor, in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract*. Published online before print April 18, 2013. DOI: 10.3810/hp.2013.04.1020.
29. Ferranini E, Ramos SJ, Salsali AM, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise. *Diabetes Care*. 2010;33(10):2217-24.
30. Bailey CJ, Iqbal N, T'Joel C, List JF. Dapagliflozin monotherapy in drug-naïve patients with diabetes: a randomized-controlled trial of low-dose range. *Diabetes Obes Metab*. Oct 2012;14(10):951-9.
31. Bailey CJ, Morales Villegas EC, Woo V, Tang W, Ptaszynska A, List JF. Efficacy and safety of dapagliflozin monotherapy in people with Type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. *Diabet Med*. 2015 Apr;32(4):531-41.
32. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomized controlled trial. *Int J Clin Pract*. May 2012;66(5):446-56.
33. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2013 Nov;1(3):208-19.
34. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2014 May;2(5):369-84. doi: 10.1016/S2213-8587(13)70208-0.
35. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, et al. DIA 2001 Study Group. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care*. 2012 Jun;35(6):1232-8.
36. Lavallo-González FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 2013; 56:2582–2592.
37. Neal B, Perkovic V, de Zeeuw D, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. *Diabetes Care*. 2015 Mar;38(3):403-11.
38. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 2013;382(9896):941-950.
39. Leiter LA, Yoon KH, Arias P, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. *Diabetes Care*. 2015 Mar;38(3):355-64.
40. Rosenstock J, Chuck L, González-Ortiz M, et al. Initial Combination Therapy With Canagliflozin Plus Metformin Versus Each Component as Monotherapy for Drug-Naïve Type 2 Diabetes. *Diabetes Care*. 2016 Mar;39(3):353-62.
41. Nauck, MA, Del Prato S, Meier JJ. Dapagliflozin vs glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care*. 2011;34(9):2015-22.
42. Del Prato S, Nauck M, Durán-García S, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. *Diabetes Obes Metab*. 2015 Jun;17(6):581-90.
43. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2010;375:2223-33.
44. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List FJ. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. *BMC Medicine*. 2013;11:43.

45. Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab.* 2012 March;97(3):1020-31.
46. Strojek K, Yoon KH, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab.* 2011;13:928-38.
47. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. *Diabetes Care.* 2012;35:1473-8.
48. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared to sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea [published online ahead of print April 5, 2013]. *Diabetes Care.* <http://dx.doi.org/10.2337/dc12-2491> and online supplement available at: <http://care.diabetesjournals.org/content/suppl/2013/04/03/dc122491.DC1/DC122491SupplementaryData.pdf>.
49. Jabbour A, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care.* 2014. Jan 15 [Epub ahead of print].
50. Cefalu WT, Leiter LA, de Bruin TW, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin's Effects on Glycemia and Cardiovascular Risk Factors in High-Risk Patients With Type 2 Diabetes: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study With a 28-Week Extension. *Diabetes Care.* 2015 Jul;38(7):1218-27.
51. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care.* 2015 Mar;38(3):376-83.
52. Wilding JP, Woo V, Soler N, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. *Ann Intern Med.* 2012;156:405-415.
53. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care.* 2014 Jun;37(6):1650-9. doi: 10.2337/dc13-2105.
54. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol.* 2014 Sep;2(9):691-700. doi: 10.1016/S2213-8587(14)70120-2.
55. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle HJ et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care.* 2013 Nov;36(11):3396-404.
56. Kovacs CS, Seshiah V, Swallow R, Jones R, Rattunde H, Woerle HJ et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab.* 2014 Feb;16(2):147-58. doi: 10.1111/dom.12188.
57. Rosenstock J, Jelaska A, Zeller C, et al. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab.* 2015 Oct;17(10):936-48.
58. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015 Nov 26;373(22):2117-28.
59. Mearns ES, Sobieraj DM, White CM, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One.* 2015 Apr 28;10(4):e0125879.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Sulfonylureas
AHFS Class 682020
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The sulfonylureas are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹⁻⁷ They stimulate the release of insulin from functioning pancreatic beta cells.¹⁻⁷ There may also be additional extrapancreatic effects; however, the mechanism by which these agents lower blood glucose during long-term administration has not been clearly established. The sulfonylureas block ATP-dependent potassium channels in pancreatic beta cells. This leads to depolarization of the beta cell, followed by an influx of calcium and stimulation of insulin secretion.⁸

The sulfonylureas may be further classified as first generation or second generation agents. The first generation sulfonylureas include chlorpropamide, tolazamide, and tolbutamide. The second generation sulfonylureas include glimepiride, glipizide, and glyburide. The second generation agents have structural characteristics that allow them to be given in much lower doses than the first generation agents. The sulfonylureas primarily differ in their pharmacokinetic parameters; however, they appear to have similar glucose-lowering effects when administered in equipotent doses.⁸ Glipizide and glyburide are also available in combination with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.^{5,7}

The sulfonylureas that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the sulfonylureas are available in a generic formulation, including the fixed-dose combination products. This class was last reviewed in February 2015.

Table 1. Sulfonylureas Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Chlorpropamide	tablet	N/A	chlorpropamide
Glimepiride	tablet	Amaryl ^{®*}	glimepiride
Glipizide	extended-release tablet, tablet	Glucotrol ^{®*} , Glucotrol XL ^{®*}	glipizide, glipizide extended-release
Glyburide	tablet	N/A	glyburide
Glyburide, micronized	tablet	Glynase ^{®*}	glyburide, micronized
Tolazamide	tablet	N/A	tolazamide
Tolbutamide	tablet	N/A	tolbutamide
Combination Products			
Glipizide and metformin	tablet	N/A	glipizide and metformin
Glyburide, micronized and metformin	tablet	Glucovance ^{®*}	glyburide, micronized and metformin

*Generic is available in at least one dosage form or strength.

PDL=Preferred Drug List

N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Sulfonylureas

Clinical Guideline	Recommendation(s)
<p>American Diabetes Association: Standards of Medical Care in Diabetes (2016)⁹</p>	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <p>Prevention or delay of type 2 diabetes</p> <ul style="list-style-type: none"> An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus. Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p>Glycemic goals in adults</p> <ul style="list-style-type: none"> Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p>Pharmacologic therapy for type 1 diabetes</p> <ul style="list-style-type: none"> Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. Most patients should use of insulin analogs to reduce hypoglycemia risk. Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. <p>Pharmacologic therapy for type 2 diabetes</p> <ul style="list-style-type: none"> At the time of diagnosis, initiate metformin therapy along with lifestyle

Clinical Guideline	Recommendation(s)
	<p>interventions, unless metformin is contraindicated.</p> <ul style="list-style-type: none"> • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If the A_{1c} target is not achieved after approximately three months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • <u>Pregestational Diabetes</u> <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1c} <6.5%, to reduce the risk of congenital anomalies. ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. • <u>Gestational Diabetes Mellitus</u> <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. • <u>General Principles for Management of Diabetes in Pregnancy</u> <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. • Due to increased red blood cell turnover, A_{1c} is lower in normal pregnancy than in normal nonpregnant women. The A_{1c} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug.

Clinical Guideline	Recommendation(s)
<p>Patient-Centered Approach (2012 and 2015 Update)^{10,11}</p>	<ul style="list-style-type: none"> • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p>

Clinical Guideline	Recommendation(s)																																																																																																									
	<ul style="list-style-type: none"> Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. <p>Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations</p> <table border="1"> <tr> <td>Initial Drug Monotherapy</td> <td colspan="6">Metformin</td> </tr> <tr> <td>Efficacy (↓HbA_{1c})</td> <td colspan="6">High</td> </tr> <tr> <td>Hypoglycemia</td> <td colspan="6">Low risk</td> </tr> <tr> <td>Weight</td> <td colspan="6">Neutral/loss</td> </tr> <tr> <td>Side Effects</td> <td colspan="6">Gastrointestinal/lactic acidosis</td> </tr> <tr> <td colspan="7">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td> </tr> <tr> <td>Two Drug Combinations</td> <td>Metformin + sulfonylurea</td> <td>Metformin + thiazolidinedione (TZD)</td> <td>Metformin + DPP-4 inhibitor</td> <td>Metformin + SGLT2 inhibitor</td> <td>Metformin + GLP-1 receptor agonist</td> <td>Metformin + insulin (usually basal)</td> </tr> <tr> <td>Efficacy (↓HbA_{1c})</td> <td>High</td> <td>High</td> <td>Intermediate</td> <td>Intermediate</td> <td>High</td> <td>Highest</td> </tr> <tr> <td>Hypoglycemia</td> <td>Moderate risk</td> <td>Low risk</td> <td>Low risk</td> <td>Low risk</td> <td>Low risk</td> <td>High risk</td> </tr> <tr> <td>Weight</td> <td>Gain</td> <td>Gain</td> <td>Neutral</td> <td>Loss</td> <td>Loss</td> <td>Gain</td> </tr> <tr> <td>Major Side Effects</td> <td>Hypoglycemia</td> <td>Edema, heart failure, bone fracture</td> <td>Rare</td> <td>Genitourinary, dehydration</td> <td>Gastrointestinal</td> <td>Hypoglycemia</td> </tr> <tr> <td colspan="7">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td> </tr> <tr> <td>Three Drug Combinations</td> <td>Metformin + sulfonylurea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin</td> <td>Metformin + TZD + Sulfonylurea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin</td> <td>Metformin + DPP-4 inhibitor + Sulfonylurea, TZD, SGLT2 inhibitor, or insulin</td> <td>Metformin + SGLT2 inhibitor + Sulfonylurea, TZD, DPP-4 inhibitor, or insulin</td> <td>Metformin + GLP-1 receptor agonist + Sulfonylurea, TZD, or insulin</td> <td>Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist</td> </tr> <tr> <td colspan="7">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td> </tr> <tr> <td>More Complex Insulin Strategies</td> <td colspan="6">Combination injectable therapy</td> </tr> </table>	Initial Drug Monotherapy	Metformin						Efficacy (↓HbA_{1c})	High						Hypoglycemia	Low risk						Weight	Neutral/loss						Side Effects	Gastrointestinal/lactic acidosis						If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)							Two Drug Combinations	Metformin + sulfonylurea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)	Efficacy (↓HbA_{1c})	High	High	Intermediate	Intermediate	High	Highest	Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk	Weight	Gain	Gain	Neutral	Loss	Loss	Gain	Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia	If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)							Three Drug Combinations	Metformin + sulfonylurea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + TZD + Sulfonylurea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + DPP-4 inhibitor + Sulfonylurea, TZD, SGLT2 inhibitor, or insulin	Metformin + SGLT2 inhibitor + Sulfonylurea, TZD, DPP-4 inhibitor, or insulin	Metformin + GLP-1 receptor agonist + Sulfonylurea, TZD, or insulin	Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist	If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents							More Complex Insulin Strategies	Combination injectable therapy					
Initial Drug Monotherapy	Metformin																																																																																																									
Efficacy (↓HbA_{1c})	High																																																																																																									
Hypoglycemia	Low risk																																																																																																									
Weight	Neutral/loss																																																																																																									
Side Effects	Gastrointestinal/lactic acidosis																																																																																																									
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)																																																																																																										
Two Drug Combinations	Metformin + sulfonylurea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)																																																																																																				
Efficacy (↓HbA_{1c})	High	High	Intermediate	Intermediate	High	Highest																																																																																																				
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk																																																																																																				
Weight	Gain	Gain	Neutral	Loss	Loss	Gain																																																																																																				
Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genitourinary, dehydration	Gastrointestinal	Hypoglycemia																																																																																																				
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)																																																																																																										
Three Drug Combinations	Metformin + sulfonylurea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + TZD + Sulfonylurea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + DPP-4 inhibitor + Sulfonylurea, TZD, SGLT2 inhibitor, or insulin	Metformin + SGLT2 inhibitor + Sulfonylurea, TZD, DPP-4 inhibitor, or insulin	Metformin + GLP-1 receptor agonist + Sulfonylurea, TZD, or insulin	Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist																																																																																																				
If combination therapy that includes basal insulin has failed to achieve HbA _{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents																																																																																																										
More Complex Insulin Strategies	Combination injectable therapy																																																																																																									
<p>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus</p>	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. 																																																																																																									

Clinical Guideline	Recommendation(s)
(2012) ¹²	<ul style="list-style-type: none"> It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.
<p>American Association of Clinical Endocrinologists/ American College Of Endocrinology; Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015)¹³</p>	<p>Antihyperglycemic pharmacotherapy for type 2 diabetes</p> <ul style="list-style-type: none"> The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement. Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists; Consensus Statement on the Comprehensive Type 2 Diabetes Management</p>	<p>Principles underlying the algorithm</p> <ul style="list-style-type: none"> Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. Achieving an HbA_{1c} \leq6.5% is recommended as the primary goal if it can be

Clinical Guideline	Recommendation(s)
<p>Algorithm 2016 (2016)¹⁴</p>	<p>achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time.</p> <ul style="list-style-type: none"> • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • The therapeutic regimen should be as simple as possible to optimize adherence. <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ Sodium glucose cotransporter 2 (SGLT-2) inhibitors. ○ DPP-4 inhibitors. ○ . ○ TZDs (use with caution). ○ Alpha-glucosidase inhibitors. • sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ DPP-4 inhibitors. ○ TZD. ○ Basal insulin. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Three-drug combination therapy</u></p> <ul style="list-style-type: none"> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or

Clinical Guideline	Recommendation(s)
	<p>combination therapy with one other agent.</p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Insulin therapy algorithm</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <p><u>Basal insulin</u></p> <ul style="list-style-type: none"> • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p><u>Basal-bolus insulin regimens</u></p> <ul style="list-style-type: none"> • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. <p><u>Basal insulin and incretin therapy regimens</u></p> <ul style="list-style-type: none"> • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last updated July 2016)¹⁵</p>	<p><u>Individualized care</u></p> <ul style="list-style-type: none"> • Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective. • Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p><u>HbA_{1c} targets</u></p> <ul style="list-style-type: none"> • Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. • For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. • In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> ○ reinforce advice about diet, lifestyle and adherence to drug treatment and ○ support the person to aim for an HbA_{1c} level of 7.0% and ○ intensify drug treatment. • Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> ○ who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy ○ for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job ○ for whom intensive management would not be appropriate, for example, people with significant comorbidities. • If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p><u>Drug treatment</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost • If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. • Initial drug treatment <ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m²: <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p><u>First intensification of drug treatment</u></p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. • Treatment with combinations of medicines including sodium–glucose

Clinical Guideline	Recommendation(s)
	<p>cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes.</p> <p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment. • If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. • Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in six months). • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment. • In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p>Insulin-based treatments</p> <ul style="list-style-type: none"> • When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional. • When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. • Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: <ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals. ○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes: <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. • Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). • Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)¹⁶</p>	<ul style="list-style-type: none"> • Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize

Clinical Guideline	Recommendation(s)
	<p>health outcomes far more than a strategy that is limited to just one or two of these clinical domains.</p> <ul style="list-style-type: none"> • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. • Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes (2012)¹⁷</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> • Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. • Match the timing of medication (including insulin) and meals. • Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. • Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals. • Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. • Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> • Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. • A lower HbA_{1c} target may be considered if it is easily and safely achieved. • A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> • Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. • Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. • First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. • Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering mediations (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)¹⁸</p>	<ul style="list-style-type: none"> • Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations ≥ 250 mg/dL. ○ Whose HbA_{1c} is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or

Clinical Guideline	Recommendation(s)
	<p>nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.</p> <ul style="list-style-type: none"> • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic “screen time” to less than two hours a day.
<p>National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November 2016)¹⁹</p>	<p>Education and information for children and young people with type 1 diabetes</p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. • Tailor the education programme to each child or young person with type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. • Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Encourage children and young people with type 1 diabetes to wear or carry something that identifies them as having type 1 diabetes (e.g., a bracelet). • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. • Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p><u>Insulin therapy for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. • Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen. • Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. • Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. • Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. • Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin infusion users. • Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. • Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin (0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%. • Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. • Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with type 1 diabetes a review of injection sites at each clinic visit. • Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. • If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily injections, continuous subcutaneous insulin infusion [CSII or insulin pump] therapy or once-, twice- or three-times daily mixed insulin injections). <p><u>Oral medicines for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. • Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. <p><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. • Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. • Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. • Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain. <p><u>Education and information for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ HbA_{1c} monitoring and targets ○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control ○ the aims of metformin therapy and possible adverse effects ○ the complications of type 2 diabetes and how to prevent them. • Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as:

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. <ul style="list-style-type: none"> ● Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every 2 years. ● Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. ● Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. ● Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible government disability benefits. ● Take particular care when communicating with and providing information to children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. <p><u>Dietary management for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> ● At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. ● Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. ● At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. ● Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications. ● Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. ● Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. ● At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI. ● Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. ● Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy.

Clinical Guideline	Recommendation(s)
	<p><u>Metformin</u></p> <ul style="list-style-type: none"> • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management (Published 2015; last updated July 2016)²⁰</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> • Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. • Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target. • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles ○ total glycated hemoglobin estimation (if abnormal hemoglobins). • Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. • Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia. • Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p><u>Self-monitoring of blood glucose</u></p> <ul style="list-style-type: none"> • Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least four times a day, including before each meal and before bed. • Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). • Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia. • Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. • Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy) • Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking.

Clinical Guideline	Recommendation(s)
	<p><u>Continuous glucose monitoring</u></p> <ul style="list-style-type: none"> • Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. • Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause. ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level ≥9%) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in HbA_{1c} of 2.5% or more. • For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. <p><u>Insulin regimens</u></p> <ul style="list-style-type: none"> • Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. • Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only). <p><u>Long-acting insulin</u></p> <ul style="list-style-type: none"> • Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. • Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul style="list-style-type: none"> ○ an existing insulin regimen being used by the person that is achieving their agreed targets ○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. • Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p><u>Rapid-acting insulin</u></p> <ul style="list-style-type: none"> • Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. • Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. • If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. <p><u>Mixed insulin</u></p> <ul style="list-style-type: none"> • Consider a twice-daily human mixed insulin regimen for adults with type 1

Clinical Guideline	Recommendation(s)
	<p>diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen.</p> <ul style="list-style-type: none"> Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p><u>Optimizing insulin therapy</u></p> <ul style="list-style-type: none"> For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously optimized insulin regimen, the following should be considered: <ul style="list-style-type: none"> injection technique injection sites self-monitoring skills knowledge and self-management skills nature of lifestyle psychological and psychosocial difficulties possible organic causes such as gastroparesis. Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. <p><u>Adjuncts</u></p> <ul style="list-style-type: none"> Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Check injection site condition at least annually and if new problems with blood glucose control occur.
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)²¹</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that

Clinical Guideline	Recommendation(s)
	<p>alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated.</p> <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. <p><u>Glycemic control goals</u></p> <ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p> <ul style="list-style-type: none"> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin

Clinical Guideline	Recommendation(s)
	<p>requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required.</p> <ul style="list-style-type: none"> Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the sulfonylureas are noted in Table 3.

Table 3. FDA-Approved Indications for the Sulfonylureas^{1-7,22,23}

Generic Name	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus	Adjunct to Diet to Lower the Blood Glucose in Patients with Non-insulin-dependent Diabetes Mellitus (Type II) Whose Hyperglycemia Cannot be Controlled by Diet Alone
Single Entity Agents		
Chlorpropamide	✓	
Glimepiride	✓	
Glipizide	✓	
Glyburide	✓	
Glyburide, micronized	✓	
Tolazamide		✓
Tolbutamide		✓
Combination Products		
Glipizide and metformin	✓	
Glyburide, micronized and metformin	✓	

IV. Pharmacokinetics

The pharmacokinetic parameters of the sulfonylureas are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Sulfonylureas²²

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Chlorpropamide	Not reported	60 to 90	Liver (% not reported)	Renal (80 to 90)	25 to 48
Glimepiride	100	>99	Liver (% not reported)	Renal (60), Feces (40)	9
Glipizide	100	97 to 99	Liver (% not reported)	Renal (63 to 89), Feces (11)	2 to 5
Glyburide	Not reported	99	Liver (% not reported)	Renal (50), Bile (50)	5 to 10
Glyburide, micronized	Not reported	99	Liver (% not reported)	Renal (80 to 90)	5 to 10
Tolazamide	Not reported	Not reported	Liver (% not reported)	Renal (85), Feces (7)	7
Tolbutamide	Not reported	80 to 99	Liver (% not reported)	Renal (75 to 80)	4.5 to 6.5
Combination Products					

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Glipizide and metformin	100/50 to 60	98/Negligible	Liver	Renal (10), Bile (11)/Renal (90)	2 to 4/6
Glyburide, micronized and metformin	Not reported/50 to 60	99/Negligible	Liver	Renal (80 to 90)/Renal (90)	5 to 10/6

V. Drug Interactions

Major drug interactions with the sulfonylureas are listed in Table 5.

Table 5. Major Drug Interactions with the Sulfonylureas²²

Generic Name(s)	Interaction	Mechanism
Metformin	Iodinated contrast materials, parenteral	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis. Glipizide/metformin or glyburide/metformin should not be restarted until renal function returns to normal.
Sulfonylureas	Quinolones	The hypoglycemic effect of glimepiride and glyburide may be increased by quinolones, especially in elderly patients with renal compromise. The mechanism of this interaction is unknown.
Sulfonylureas	Salicylates	Increased hypoglycemia may occur. Salicylates reduce basal plasma glucose levels and enhance insulin secretion. Inhibition of prostaglandin synthesis may inhibit acute insulin responses to glucose. Displaced sulfonylurea protein binding has been suggested.
Sulfonylureas (glimepiride, tolbutamide)	Azole antifungals	Azole antifungals may inhibit the cytochrome P450 2C9 isoenzyme-mediated metabolism of certain sulfonylureas, increasing the hypoglycemic effects.
Sulfonylureas (glyburide)	Bosentan	Bosentan may increase the metabolism (cytochrome P450 2C9 and 3A4 isoenzyme-mediated) of glyburide. Other mechanisms may also be involved. Plasma levels of bosentan and glyburide may be decreased. Increased risk of elevated liver enzymes, resulting in serious liver injury may occur.
Sulfonylureas	Disopyramide	Concurrent use of disopyramide and sulfonylureas may result in increased risk of hypoglycemia.

VI. Adverse Drug Events

The most common adverse drug events reported with the sulfonylureas are listed in Table 6. The boxed warning for glipizide/metformin and glyburide/metformin is listed in Table 7. The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This association has led to a warning and is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. However it is important to note that only tolbutamide was included in this study.^{1-7,23}

Table 6. Adverse Drug Events (%) Reported with the Sulfonylureas^{1-7,23}

Adverse Events	Single Entity Agents							Combination Products	
	Chlorpropamide	Glimepiride	Glipizide	Glyburide	Glyburide, micronized	Tolazamide	Tolbutamide	Glipizide and Metformin	Glyburide, Micronized and Metformin
Cardiovascular									
Chest discomfort	-	-	-	-	-	-	-	✓	✓
Flushing	-	-	-	-	-	-	-	✓	✓
Hypertension	-	-	-	-	-	-	-	3 to 4	-
Palpitations	-	-	-	-	-	-	-	✓	✓
Syncope	-	-	✓	-	-	-	-	✓	-
Central Nervous System									
Anxiety	-	-	✓	-	-	-	-	✓	-
Depression	-	-	✓	-	-	-	-	✓	-
Dizziness	✓	2	✓	✓	✓	✓	-	2 to 5	✓
Drowsiness	-	-	✓	-	-	-	-	✓	-
Fatigue	-	-	-	-	-	✓	-	-	-
Headache	✓	2	✓	✓	✓	✓	✓	6 to 13	6
Insomnia	-	-	✓	-	-	-	-	✓	-
Nervousness	-	-	✓	-	-	-	-	✓	-
Paresthesia	-	-	✓	✓	✓	-	-	✓	✓
Tremor	-	-	✓	-	-	-	-	✓	-
Vertigo	-	-	-	-	-	✓	-	-	-
Weakness	-	2	-	-	-	✓	-	9	9
Dermatological									
Allergic skin reactions	-	✓	✓	✓	✓	-	-	✓	✓
Angioedema	-	-	-	✓	✓	-	-	-	✓
Eczema	-	-	✓	-	-	-	-	✓	-
Erythema	✓	✓	✓	✓	✓	-	✓	✓	✓
Exfoliative dermatitis	✓	-	-	-	-	-	-	-	-
Morbilloform or	✓	✓	✓	✓	✓	✓	✓	✓	✓

Adverse Events	Single Entity Agents							Combination Products	
	Chlorpropamide	Glimepiride	Glipizide	Glyburide	Glyburide, micronized	Tolazamide	Tolbutamide	Glipizide and Metformin	Glyburide, Micronized and Metformin
maculopapular eruptions									
Photosensitivity	✓	✓	✓	✓	✓	✓	✓	✓	✓
Porphyria cutanea tarda	✓	✓	✓	✓	✓	✓	-	✓	✓
Pruritus	✓	✓	✓	✓	✓	✓	✓	✓	✓
Purpura	-	-	-	✓	✓	-	-	-	✓
Rash	-	✓	✓	✓	✓	✓	✓	✓	✓
Sweating	-	-	✓	-	-	-	-	✓	✓
Urticaria	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vasculitis	-	✓	-	✓	✓	-	-	✓	✓
Endocrine and Metabolic									
Edema	-	✓	✓	-	-	-	-	✓	-
Hypoglycemia	✓	1 to 2	✓	✓	✓	✓	✓	✓	✓
Hyponatremia	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lactic acidosis	-	-	-	-	-	-	-	✓	✓
Syndrome of inappropriate antidiuretic hormone	✓	✓	✓	✓	✓	✓	✓	✓	✓
Gastrointestinal									
Abdominal/gastrointestinal pain	-	✓	-	-	-	-	-	6	6
Anorexia	✓	✓	✓	✓	✓	✓	-	✓	-
Constipation	-	✓	✓	✓	✓	✓	-	✓	✓
Diarrhea	✓	✓	✓	✓	✓	✓	-	2 to 53	10 to 53
Dyspepsia	-	-	-	-	-	-	-	✓	✓
Epigastric fullness	-	✓	✓	✓	✓	✓	✓	✓	✓
Flatulence	-	-	✓	-	-	-	-	12	12
Gastralgia	-	-	✓	-	-	-	-	✓	-
Heartburn	-	✓	✓	✓	✓	✓	✓	✓	✓
Hunger	✓	-	-	-	-	-	-	-	-
Indigestion	-	-	-	-	-	-	-	7	7
Nausea	✓	1	✓	✓	✓	✓	✓	1 to 26	7 to 26
Proctocolitis	✓	-	-	-	-	-	-	-	-
Taste alteration	-	-	-	-	-	-	✓	✓	✓
Vomiting	✓	✓	✓	-	-	✓	-	1 to 26	7 to 26
Genitourinary									
Diuresis	-	✓	✓	✓	✓	✓	-	✓	-

Adverse Events	Single Entity Agents							Combination Products	
	Chlorpropamide	Glimepiride	Glipizide	Glyburide	Glyburide, micronized	Tolazamide	Tolbutamide	Glipizide and Metformin	Glyburide, Micronized and Metformin
Dysuria	-	-	-	-	-	-	-	✓	-
Urinary tract infection	-	-	-	-	-	-	-	1	-
Hematologic									
Agranulocytosis	✓	✓	✓	✓	✓	✓	✓	✓	-
Aplastic anemia	✓	✓	✓	✓	✓	✓	✓	✓	-
Blood dyscrasias	-	-	✓	-	-	-	-	✓	-
Eosinophilia	✓	-	-	-	-	-	-	-	-
Hemolytic anemia	✓	✓	✓	✓	✓	✓	✓	✓	✓
Leukopenia	✓	✓	✓	✓	✓	-	✓	✓	-
Megaloblastic anemia	-	-	-	-	-	-	-	✓	✓
Pancytopenia	✓	✓	✓	✓	✓	-	-	✓	-
Thrombocytopenia	✓	✓	✓	✓	✓	✓	✓	✓	-
Hepatic									
Cholestatic jaundice	✓	✓	✓	✓	✓	✓	✓	✓	✓
Elevated liver enzyme levels	-	✓	-	-	-	-	-	-	-
Hepatic porphyria	✓	✓	✓	-	-	✓	✓	✓	-
Hepatitis	-	✓	-	✓	✓	-	-	-	✓
Liver function abnormalities	-	✓	-	✓	✓	-	-	-	✓
Transaminases increased	-	-	-	✓	✓	-	-	-	✓
Musculoskeletal									
Arthralgia	-	-	✓	✓	✓	-	-	✓	-
Leg cramps	-	-	✓	-	-	-	-	✓	-
Musculoskeletal pain	-	-	-	-	-	-	-	8	-
Myalgia	-	-	✓	✓	✓	-	-	✓	✓
Respiratory									
Pneumonitis	-	-	-	-	-	-	-	✓	✓
Rhinitis	-	-	✓	-	-	-	-	✓	-
Upper respiratory tract infection	-	-	-	-	-	-	-	✓	✓
Other									
Blurred vision	-	✓	✓	✓	✓	-	-	✓	✓
Changes in accommodation	-	✓	-	✓	✓	-	-	✓	✓

Adverse Events	Single Entity Agents							Combination Products	
	Chlorpropamide	Glimepiride	Glipizide	Glyburide	Glyburide, micronized	Tolazamide	Tolbutamide	Glipizide and Metformin	Glyburide, Micronized and Metformin
Chills	-	-	-	-	-	-	-	✓	✓
Decreased Vitamin B ₁₂ levels	-	-	-	-	-	-	-	✓	✓
Disulfiram-like reaction	✓	✓	✓	✓	✓	✓	✓	✓	✓
Flu-like symptoms	-	-	-	-	-	-	-	✓	✓
Hypersensitivity reaction	-	-	-	✓	✓	-	✓	✓	✓
Nail disorder	-	-	-	-	-	-	-	✓	✓
Pain	-	-	✓	-	-	-	-	✓	-

✓ Percent not specified.
-Event not reported.

Table 7. Boxed Warning for Glipizide and metformin and Glyburide, micronized and metformin⁷

WARNING

Lactic acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur because of metformin accumulation during treatment with glipizide/metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (more than 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels of more than 5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases per 1,000 patient-years, with approximately 0.015 fatal cases per 1,000 patient-years). In more than 20,000 patient-years of exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal function impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure (CHF) requiring pharmacologic management, in particular those with unstable or acute CHF who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal function impairment and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and the use of the minimum effective dose of metformin. In particular, accompany the treatment of elderly patients with careful monitoring of renal function. Do not initiate glipizide/metformin treatment in patients 80 years of age and older unless measurement of creatinine clearance demonstrates that renal function is not reduced, because these patients are more susceptible to developing lactic acidosis. In addition, promptly withhold glipizide/metformin in the presence of any condition associated with dehydration, hypoxemia, or sepsis. Because hepatic function impairment may significantly limit the ability to clear lactate, generally avoid glipizide/metformin in patients with clinical or laboratory evidence of hepatic disease. Caution patients against excessive alcohol intake, acute or chronic, when taking glipizide/metformin, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, temporarily discontinue glipizide/metformin prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis is often subtle and accompanied only by nonspecific symptoms, such as increasing somnolence, malaise, myalgia, nonspecific abdominal distress, and respiratory distress. There may be associated hypotension, hypothermia, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's health care provider must be aware of the possible importance of such symptoms. Instruct the patient to notify their health care provider immediately if symptoms occur. Withdraw glipizide/metformin until the situation is clarified. Serum electrolytes, ketones, blood glucose, and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of glipizide/metformin, gastrointestinal symptoms, which are common during initiation of therapy with metformin, are unlikely to be drug-related. Later occurrence of gastrointestinal symptoms could be caused by lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking glipizide/metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Suspect lactic acidosis in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (e.g., ketonemia, ketonuria).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking glipizide/metformin, discontinue the drug immediately and institute general supportive measures promptly. Because metformin is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

VII. Dosing and Administration

The usual dosing regimens for the sulfonylureas are listed in Table 8.

Table 8. Usual Dosing Regimens for the Sulfonylureas^{1-7,23}

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Chlorpropamide	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 100 to 225 mg QD; maintenance, 100 to 500 mg/day	Safety and efficacy in children have not been established.	Tablet: 100 mg 250 mg
Glimepiride	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 1 or 2 mg QD; maximum, 8 mg/day	Not recommended in pediatric patients.	Tablet: 1 mg 2 mg 4 mg
Glipizide	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Extended-release tablet: initial, 5 mg QD; maintenance, 5 to 10 mg QD; maximum, 20 mg/day Tablet: initial, 2.5 or 5 mg QD; maximum, 40 mg/day	Safety and efficacy in children have not been established.	Extended-release tablet: 2.5 mg 5 mg 10 mg Tablet: 5 mg 10 mg
Glyburide	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 1.25 to 5 mg QD; maintenance, 1.25 to 20 mg/day; maximum, 20 mg/day	Safety and efficacy in children have not been established.	Tablet: 1.25 mg 2.5 mg 5 mg
Glyburide, micronized	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: initial, 0.75 to 3 mg QD; maintenance, 0.75 to 12 mg QD; maximum, 12 mg/day	Safety and efficacy in children have not been established.	Tablet: 1.5 mg 3 mg 6 mg
Tolazamide	<u>Adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be controlled by diet alone:</u> Tablet: initial, 100 to 250 mg QD; maintenance, 100 to 1,000 mg QD; maximum, 1,000 mg/day	Safety and efficacy in children have not been established.	Tablet: 250 mg 500 mg
Tolbutamide	<u>Adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be controlled by diet alone:</u> Tablet: initial, 1 to 2 g/day; maintenance, 0.25 to 3 g/day; maximum, 3 g/day	Safety and efficacy in children have not been established.	Tablet: 500 mg
Combination Products			
Glipizide and	<u>Adjunct to diet and exercise to improve</u>	Safety and efficacy in	Tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
metformin	<u>glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: dosage must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20-2,000 mg	children have not been established.	2.5-250 mg 2.5-500 mg 5-500 mg
Glyburide, micronized and metformin	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u> Tablet: dosage must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20-2,000 mg	Safety and efficacy in children have not been established.	Tablet: 1.25-250 mg 2.5-500 mg 5-500 mg

QD=once daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the sulfonylureas are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Sulfonylureas

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
United Kingdom Prospective Diabetes Study Group ²⁴ (1998) Chlorpropamide 100 to 500 mg daily vs glibenclamide* 2.5 to 20 mg daily vs glipizide 2.5 to 40 mg daily vs insulin vs conventional therapy with diet	RCT Patients newly diagnosed with type 2 diabetes, baseline HbA _{1c} 7.05% in the dietary treatment group and 7.09% in the intensive therapy group	N=3,867 10 years	Primary: Time to the first occurrence of any diabetes-related endpoint, time to diabetes-related death, all-cause mortality Secondary: MI, sudden death, stroke, amputation or death due to peripheral vascular disease, microvascular complications, retinopathy, vitreous hemorrhage, and/or fatal or nonfatal renal failure	Primary: There was a 12% risk reduction (95% CI, 1 to 21; P=0.029) for any diabetes-related end point, 10% risk reduction (95% CI, -11 to 27; P=0.34) for any diabetes-related death, and a 6% risk reduction (95% CI, -10 to 20; P=0.44) for all-cause mortality when intensive therapy (sulfonylurea or insulin) was compared to conventional therapy with diet. Patients receiving an intensive treatment (sulfonylurea or insulin) had a 25% risk reduction (95% CI, 7 to 40; P=0.0099) in microvascular end points compared to conventional therapy with diet. Most of this reduction was due to fewer cases of retinal photocoagulation. There were no differences between the intensive and conventional treatment groups or between the three intensive treatment groups in the number of patients who had a silent MI, cardiomegaly, evidence of peripheral vascular disease, or absent peripheral pulses. Secondary: There was no significant difference between chlorpropamide, insulin, and glibenclamide in macrovascular events. There was no significant difference between the three intensive treatments in microvascular end points or in the risk reduction for retinal photocoagulation.
Feinbock et al. ²⁵ (2003)	MC, OL, PG, RCT Patients from 36 to	N=219 20 weeks	Primary: Number of responders in each	Primary: Glimepiride treatment was associated with a significant responder rate compared to acarbose, 61 vs 34% respectively (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Glimepiride 1 to 6 mg QD</p> <p>vs</p> <p>acarbose 50 to 200 mg TID</p>	<p>80 years of age with type 2 diabetes uncontrolled on diet alone, with an HbA_{1c} ≥7.8%, and a BMI 24 to 35 kg/m²</p>		<p>group (defined as a FPG ≤7.8 mmol/L at the final visit)</p> <p>Secondary: Changes in HbA_{1c}, weight, PPG, and C-peptide levels from baseline</p>	<p>Glimepiride resulted in significant decreases in HbA_{1c} (2.5±2.2%) as compared to acarbose (1.8±2.2%; P=0.014).</p> <p>Secondary: FPG levels were significantly decreased with glimepiride as compared to acarbose (2.6±2.6 mmol/L vs 1.4±2.8 mmol/L; P=0.004).</p> <p>There was a greater reduction in HbA_{1c} in the glimepiride group (2.5±2.2%) compared to the acarbose group (1.8±2.2%; P=0.014).</p> <p>Decreased glucose response to breakfast was significant for glimepiride compared to acarbose (P=0.0001).</p> <p>Weight loss was observed in the acarbose group (P=0.001) and glimepiride group (P=0.8) from baseline.</p> <p>C-peptide levels were higher in the glimepiride group compared to the acarbose group at study end point (5.44±2.26 ng/mL vs 4.57±1.93 ng/mL; P=0.0004; intra-individual difference: 0.53±1.7 ng/mL vs -0.31±1.72 ng/mL; P=0.002).</p>
<p>Martin et al.²⁶ (2003)</p> <p>Glimepiride</p> <p>vs</p> <p>glibenclamide*</p>	<p>MC, OS</p> <p>Drug treatment-naïve patients ≥35 years of age with a confirmed type 2 diabetes diagnosis who with or without dieting received initial dose adjustment with glimepiride or glibenclamide during the study period from April 1998 to March</p>	<p>N=520</p> <p>1 year ±3 months</p>	<p>Primary: Mean change in body weight and BMI</p> <p>Secondary: Changes in HbA_{1c}, FPG, cholesterol</p>	<p>Primary: Both treatments led to significant reductions in body weight and BMI over the observed treatment period as compared to baseline (P<0.01).</p> <p>Mean weight loss from baseline to end point was greater with glimepiride compared to glibenclamide (-2.04±3.99 vs -0.58±3.65 kg, respectively; P<0.001). The variability of the changes between centers was significant (P<0.001), the differences between the treatment arms in change in body weight from baseline was still significant (P=0.027) if the centers were taken into account as an additional factor. Glimepiride achieved a greater reduction in BMI compared to glibenclamide over the observed period (-0.72±1.38 vs -0.20±1.28 kg/m², respectively; P<0.001).</p> <p>Secondary: There were significant decreases from baseline in FPG and HbA_{1c} from</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	1999, disease duration <5 years, BMI ≥ 27 kg/m ² , patients before or during the study were not taking any antidiabetic medications other than glimepiride or glibenclamide or any other medication known to influence body weight			<p>baseline for both groups (P<0.001). The mean change from baseline for HbA_{1c} was -1.23±0.09% for glimepiride and -1.26±0.09% for glibenclamide. The mean change from baseline for FPG was -2.43±0.24 mmol/L for glimepiride and -3.03±0.24 mmol/L for glibenclamide.</p> <p>Changes from baseline for TC were significant for both groups (P<0.001). The change was -0.31±0.06 mmol/L for glimepiride and -0.29±0.06 mmol/L for glibenclamide.</p> <p>Change from baseline for HDL-C were 0.07±0.02 mmol/L for glimepiride (P=0.004) and -0.02±0.04 mmol/L for glibenclamide (P=0.924).</p> <p>Change from baseline for LDL-C was -0.21±0.06 mmol/L for glimepiride (P=0.001) and -0.33±0.07 mmol/L for glibenclamide (P<0.001).</p> <p>Change from baseline for TG was -0.03±0.12 mmol/L for glimepiride (P=0.111) and -0.29±0.09 mmol/L for glibenclamide (P<0.001).</p>
<p>Garber et al.²⁷ (2009) LEAD-3</p> <p>Liraglutide 1.2 and 1.8 mg SC QD</p> <p>vs</p> <p>glimepiride 8 mg/day</p>	<p>AC, DB, DD, MC, PG, RCT</p> <p>Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥ 2</p>	<p>N=746</p> <p>52 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline body weight, FPG, eight-point self-measured glucose concentrations, BP, β cell function, fasting glucagon, and patient-reported QOL</p>	<p>Primary: Decreases in HbA_{1c} were -0.84±1.23% with liraglutide 1.2 mg, -1.14±1.24% with liraglutide 1.8 mg, and -0.51±1.20% with glimepiride. Decreases with liraglutide were significantly greater compared to glimepiride. Differences between glimepiride and liraglutide 1.2 mg were -0.62% (95% CI, -0.83 to -0.42; P<0.0001) and liraglutide 1.8 mg were -0.33% (95% CI, -0.53 to -0.13; P=0.0014). Additionally, decreases with liraglutide 1.8 mg were significantly greater compared to liraglutide 1.2 mg (-0.29%; 95% CI, -0.50 to -0.09; P=0.0046).</p> <p>Secondary: Liraglutide-treated patients lost body weight and those receiving glimepiride gained weight (P values not reported). The weight loss with liraglutide after 16 weeks was sustained throughout the 52 weeks.</p> <p>Decreases in FPG with liraglutide (1.2 mg, -0.84 mmol/L; P=0.027 and 1.8 mg, -1.42 mmol/L; P=0.0001) were significantly greater compared to glimepiride (-0.29 mmol/L).</p> <p>Decreases in PPG occurred with all three treatments (liraglutide 1.2 mg vs</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)</p>			<p>glimepiride; P=0.1616, liraglutide 1.8 mg vs glimepiride; P=0.0038, and liraglutide 1.8 mg vs liraglutide 1.2 mg; P=0.1319).</p> <p>Decreases in SBP were -0.7 mm Hg with glimepiride compared to -0.1 mm Hg with liraglutide 1.2 mg (P=0.2912) and -3.6 mm Hg with liraglutide 1.8 mg (P<0.0118). Mean DBP decreased but not significantly with any treatment.</p> <p>HOMA-IR and fasting glucagon significantly decreased with liraglutide, but increased with glimepiride. HOMA-IR was decreased by -0.65% with liraglutide 1.2 mg and by -1.35% with liraglutide 1.8 mg, and increased by 0.85% with glimepiride (P=0.0249 and P=0.0011 for liraglutide 1.2 and 1.8 mg vs glimepiride).</p> <p>Patients receiving liraglutide 1.8 mg reported improved QOL scoring for physical and emotional domains compared to glimepiride (P=0.02). Improvements were largely as a result of improvements in weight image and weight concern (P<0.01).</p>
<p>Garber et al.²⁸ (2011) LEAD-3 Liraglutide 1.2 mg and 1.8 mg SC QD vs glimepiride 8 mg/day</p>	<p>ES (LEAD-3²⁸) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥ 2</p>	<p>N=440 52 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline body weight, FPG, β cell function, fasting glucagon, and BP</p>	<p>Primary: The decrease in HbA_{1c} was significantly greater with liraglutide 1.2 mg (-0.9 vs -0.6%; P=0.0376) and 1.8 mg (-1.1 vs -0.6%; P=0.0016) compared to glimepiride over two years of treatment.</p> <p>Secondary: Over two years, patients receiving liraglutide 1.2 or 1.8 mg experienced weight loss compared to weight gain with patients receiving glimepiride (-2.3 and -2.8 vs 1.0 kg, respectively; P<0.001 for both comparisons).</p> <p>Compared to glimepiride (-1.8 mmol/L), both liraglutide 1.2 (-1.9 mmol/L) and 1.8 mg (-2.6 mmol/L) were significantly more effective at decreasing FPG over the course of the extension period (P=0.0015 and P=0.0001, respectively).</p> <p>In patients who completed two years of treatment, baseline HOMA-IR decreased by -1.1% with liraglutide 1.2 mg and -0.8% with liraglutide 1.8 mg, and increased by 0.8% with glimepiride (P=0.0451 for liraglutide 1.2 mg vs glimepiride).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)</p>			<p>The proinsulin:insulin ratio increased slightly with all treatments, by 0.108 with liraglutide 1.2 mg, 0.018 with liraglutide 1.8 mg, and 0.141 with glimepiride (P values not reported).</p> <p>After two years, all three treatments had increases in HOMA-B, fasting insulin, and fasting C-peptide; and had decreases in fasting glucagon, but there were no differences between treatments (P values not reported).</p> <p>No differences between treatments in change in pulse, DBP, and SBP were observed in any patient completing two years of treatment.</p>
<p>Bode et al.²⁹ (2010) LEAD-3</p> <p>Liraglutide 1.2 and 1.8 mg SC QD</p> <p>vs</p> <p>glimepiride 8 mg/day</p>	<p>Post-hoc analysis (LEAD-3²⁸)</p> <p>Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥ 2 months and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering</p>	<p>N=746</p> <p>52 weeks</p>	<p>Primary: Impact of treatment on patient-reported perceptions of body image, weight, and weight concern; psychological well-being and distress, cognitive functioning and health</p> <p>Secondary: Not reported</p>	<p>Primary: Both measures of weight perception (weight assessment and weight concern) were more favorable with liraglutide compared to glimepiride. Baseline-adjusted mean weight assessment compared to the reference point “my weight is just right” was significantly more favorable (i.e., shifted from more overweight to less overweight) with liraglutide 1.8 mg (P=0.002). Furthermore, weight concern decreased markedly with liraglutide, with mean scores significantly less compared to glimepiride (liraglutide 1.2 mg; P<0.0001 and liraglutide 1.8 mg; P<0.001).</p> <p>Logistic regression estimates indicated that patients receiving liraglutide 1.8 mg were 52% less likely to report feeling either “somewhat” or “very overweight” vs “just right”, “somewhat underweight,” or “very overweight” during treatment compared to patients receiving glimepiride (OR, 0.480; 95% CI, 0.331 to 0.696; P value not reported). Also, liraglutide 1.8 mg-treated patients were 39% less likely to report being “somewhat worried”, “very worried,” or “extremely worried” vs “a little concerned” or “not concerned at all” about their weight during treatment compared to glimepiride treated patients (OR, 0.608; 95% CI, 0.440 to 0.850; P value not reported).</p> <p>There were no differences between liraglutide and glimepiride for the body image scales (body size evaluation and body appearance distress) or for any of the cognitive functioning and performance scales during treatment (P values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	agent monotherapy)			<p>The health-related QOL composite score significantly improved more favorably with liraglutide 1.8 mg compared to glimepiride (P=0.004). Favorable improvements were seen in the composite scales of mental and emotional healthy, psychological well-being, psychological distress, and general perceived health (P<0.05 for all). The higher scores with liraglutide 1.8 mg for mental and emotional health reflected greater improvement in both domains of psychological well-being and psychological distress compared to glimepiride. There were no differences for these scales between liraglutide 1.2 mg and glimepiride (P values not reported). However, there was a significant difference between liraglutide 1.2 mg and glimepiride in general health status favoring liraglutide (P=0.006).</p> <p>Correlation analyses using data pooled from all treatments confirmed that decreases in BMI were correlated with improvements in both weight assessment and weight concern (P<0.0001 for both), indicating that patients' reports were valid representations of actual weight losses.</p> <p>Decreases in HbA_{1c} corresponded to improvements in general perceived health (P<0.0001), cognitive functioning composite score (P=0.006), and cognitive performance (P=0.004). Correlations of change in HbA_{1c} within treatment groups with change in patient-reported measures were strongest with liraglutide 1.8 mg.</p> <p>Secondary: Not reported</p>
<p>Gottschalk et al.³⁰ (2007)</p> <p>Glimepiride 1 to 8 mg QD</p> <p>vs</p> <p>metformin 500 to 1,000 mg BID</p>	<p>AC, MC, PG, RCT, SB</p> <p>Pediatric subjects 8 to 17 years of age with type 2 diabetes (HbA_{1c} >7.1 and <12.0%) with inadequate control despite treatment with either diet and exercise alone for at</p>	<p>N=285</p> <p>24 weeks</p>	<p>Primary: Mean change in HbA_{1c} from baseline to week 24</p> <p>Secondary: Mean change in HbA_{1c} from baseline to week 12, proportion of patients achieving</p>	<p>Primary: Significant reductions from baseline HbA_{1c} were seen in both the glimepiride (-0.54%, P=0.001) and metformin (-0.71%, P=0.0002) groups. No significant differences were observed between groups in reductions in HbA_{1c}.</p> <p>Secondary: Significant reductions in the adjusted mean change from baseline HbA_{1c} to week 12 were -0.69 and -0.76% in patients receiving glimepiride and metformin, respectively (P<0.05).</p> <p>A total of 42.4 and 48.1% of patients in the glimepiride and metformin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>least 2 weeks prior to randomization or diet and exercise combined with 3 months of ongoing or previous oral antidiabetic monotherapy</p>		<p>an HbA_{1c} <7.0% at week 24, mean change in fasting self monitoring blood glucose from baseline to weeks four, eight, 12, 18, and 24, mean changes in serum lipid concentrations from baseline to week 24 and changes in BMI, safety, adverse events, hypoglycemic episodes and vital signs</p>	<p>groups, respectively, achieved HbA_{1c} <7.0% at week 24 (P=0.347).</p> <p>Significant reductions were seen in fasting self monitoring blood glucose levels from baseline to weeks 18 and 24 in patients receiving metformin (P<0.05) but no similar reductions were reported in the glimepiride group.</p> <p>There were no significant differences between the glimepiride and metformin groups in the mean change from baseline in any of the serum lipid concentrations.</p> <p>Significant between-group differences were observed in the mean change from baseline BMI to week 24. Values were 0.26 kg/m² and 0.33 kg/m² in patients receiving glimepiride and metformin, respectively (P=0.003).</p> <p>No deaths occurred during the study. The proportions of patients experiencing ≥1 adverse event were comparable between both treatment groups, with the most common adverse events being hyperglycemia, upper abdominal pain, diarrhea, nausea and headache. Two patients experienced serious adverse events that were considered possibly related to treatment: one patient in the glimepiride group had hyperglycemia, diabetic ketoacidosis and increased serum osmolarity and one patient in the metformin group had a non-hypoglycemic convulsion.</p> <p>The incidence of clinically relevant hypoglycemia was similar in both groups (P=0.554).</p> <p>No clinically significant differences in vital signs were seen between treatment groups.</p>
<p>Hartley et al.³¹ (2015)</p> <p>Glimepiride vs sitagliptin</p>	<p>DB, MC, NI, RCT</p> <p>Patients ≥65 and ≤85 years of age with type 2 diabetes that was inadequately controlled with diet and exercise alone</p>	<p>N=480</p> <p>30 weeks</p>	<p>Primary:</p> <p>Change in baseline HbA_{1c}, FPG, and body weight; incidence of symptomatic hypoglycemia</p> <p>Secondary:</p>	<p>Primary:</p> <p>After 30 weeks, the least squares (LS) mean change in HbA_{1c} baseline was -0.32% with sitagliptin and -0.51% with glimepiride, for a between-group difference of 0.19% (95% CI, 0.03 to 0.34). This result met the pre-specified criterion for declaring non-inferiority. The LS mean change in FPG from baseline was -14.5 mg/dL with sitagliptin and -21.2 mg/dL with glimepiride, for a between-group difference of 6.7 mg/dL (95% CI, 0.7 to 12.7). The percentages of patients with adverse events of symptomatic hypoglycemia were 0.8% in the sitagliptin group and 4.7% in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	glimepiride group (between-treatment difference, -3.9 %; P=0.009). The LS mean change in body weight from baseline was 0.4 kg with sitagliptin and 1.1 kg with glimepiride, for a between-group difference of -0.7 kg (P=0.011). Secondary: Not reported
Go et al. ³² (2004) Glipizide XL 5 to 20 mg QD in the morning vs glipizide XL 5 to 20 mg QD in the evening vs glibenclamide* 5 to 20 mg QD in the morning vs placebo	DB, PC, RCT Patients 30 to 80 years of age with a documented diagnosis of type 2 diabetes for ≥6 months prior to the study and who had been treated with diet alone and/or sulfonylureas for at least 2 months	N=42 8 weeks	Primary: Change from baseline in hepatic glucose production Secondary: Changes in fasting and 24 hour glucose and insulin, fructosamine, HbA _{1c}	Primary: Hepatic glucose production in the patients receiving glipizide XL in the morning (P<0.05) or glibenclamide (P<0.01) was significantly reduced at the end of the study compared to baseline. There were no significant differences in hepatic glucose production found when comparing glipizide XL in the morning, glipizide XL in the evening, and glibenclamide. Secondary: Fasting and 24 hour glucose were significantly reduced from baseline to a similar degree by glipizide XL in the morning (33%; P<0.001, 39%; P<0.0001, respectively), glipizide XL in the evening (33%; P<0.0001, 32%; P<0.0001), and glibenclamide (37%; P<0.05, 37%; P<0.0001). Fructosamine and HbA _{1c} were significantly reduced from baseline by glipizide XL in the morning (28%; P<0.001, 22%; P<0.0001, respectively), glipizide XL in the evening (25%; P<0.005, 24%; P<0.005), and glibenclamide (17%; P<0.001, 14%; P<0.05). Each active treatment group improved glycemic control and resulted in beneficial effects on fructosamine and HbA _{1c} .
Birkeland et al. ³³ (1994) Glipizide vs glyburide	DB, PC, PRO, RCT Patients with non-insulin-dependent diabetes (type 2) mellitus	N=46 15 months	Primary: Changes in HbA _{1c} , PPG, fasting and postprandial insulin levels Secondary: Not reported	Primary: There was a comparable reduction in HbA _{1c} by both active treatments compared to placebo throughout the study. There was a marked initial decrease in the glipizide and glyburide groups, but all three groups showed gradually increasing HbA _{1c} levels. Glipizide and glyburide achieved and maintained lower PPG levels and increased fasting and postprandial insulin levels compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Secondary: Not reported
Burge et al. ³⁴ (1998) <u>Week 1</u> Placebo <u>Week 2</u> glipizide XL 10 mg every morning vs glyburide 10 mg every morning <u>Week 3</u> glipizide XL 20 mg every morning vs glyburide 20 mg every morning	DB, PC, PRO, RCT Patients 55 to 77 years of age with type 2 diabetes treated with oral sulfonylureas alone for ≥ 2 months	N=58 3 weeks	Primary: Development of hypoglycemia during the final nine hours of the 23-hour fast Secondary: Changes in plasma glucose, C-peptide, glucagon, catecholamine concentrations	Primary: No hypoglycemia occurred during any of the fasting studies. Secondary: Plasma glucose was significantly decreased from baseline when comparing all active treatments to placebo (P<0.001). When the dose of each agent was doubled, an additional decrease of plasma glucose was observed. Plasma glucose parameters did not differ between the two sulfonylureas. Mean and peak C-peptide levels were significantly increased compared to placebo for both treatment groups at the 10 and 20 mg doses. Mean C-peptide concentration were increased in the glyburide group compared to the glipizide XL group during the 20 mg study (P=0.05). Concentrations of glucagon and norepinephrine did not differ according to treatment group or dosage. There were no differences in plasma epinephrine concentrations according to treatment group. Baseline and nadir levels of epinephrine did not differ from placebo with active treatment. Mean and peak levels of epinephrine were significantly increased compared to placebo during both the 10 and 20 mg studies when the treatment groups were combined (P<0.001). There was no difference in epinephrine response between the 10 mg and 20 mg studies.
Chung et al. ³⁵ (2002) Glipizide 10 mg BID vs glipizide XL 20 mg QD	OL, RCT, XO Patients 42 to 71 years of age with type 2 diabetes with no significant history of hepatic, renal, gastrointestinal, or cardiovascular	N=25 1 month	Primary: Changes in pharmacokinetic parameters, serum glucose, insulin, and C-peptide levels Secondary: Not reported	Primary: For each tablet formulation, plasma glipizide concentrations at the start (C ₀) and end (C ₂₄) of the dosage interval on the fifth day were not significant (P>0.05). At two hours after the morning and evening doses of glipizide, plasma glipizide concentrations were two to four times higher with the glipizide XL at the same times. Mean glipizide maximum concentrations after glipizide were significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	disease, who were not receiving β -blockers at the time of the study and who had not received insulin for a period of more than 1 week in the 3 months before the study			higher after glipizide XL ($P \leq 0.05$). Relative bioavailability was 100% for glipizide doses and $81 \pm 22\%$ for glipizide XL. Glipizide and glipizide XL had similar effects on serum glucose levels, serum insulin levels, and C-peptide levels. Secondary: Not reported
Hseih et al. ³⁶ (2006) Glipizide XR 10 mg daily vs glipizide 5 mg BID	DB, DD, PC, PG, RCT Chinese patients 30 to 70 years of age with type 2 diabetes for ≥ 6 months and maintenance of stable diet and treatment with a sulfonylurea drug regimen for the previous 3 months	N=57 12 weeks	Primary: Change in fasting plasma glucose Secondary: Change in HbA _{1c}	Primary: In the intent-to-treat analysis, the mean changes in FPG between groups were not significantly different (P value not reported). Secondary: In the intent-to-treat analysis, the mean changes in HbA _{1c} between groups were not significantly different (P value not reported).
Kitabchi et al. ³⁷ (2000) Glipizide daily vs glyburide daily	PRO, RCT Patients with type 2 diabetes who were unresponsive to diet therapy	N=18 15 months	Primary: Changes in FPG, two-hour PPG after a standard breakfast, insulin and glucose response to test meal challenge, HbA _{1c} , glucose tolerance Secondary: Not reported	Primary: Similar doses of glipizide (11 mg/day) or glyburide (10 mg/day) resulted in comparable reduction of FPG and HbA _{1c} . Additionally, there was an increase in first phase insulin response to intravenous glucose tolerance testing. The reduction in FPG and two-hour PPG was greater with glipizide compared to glyburide in six months. Results demonstrated that glipizide and glyburide are equipotent at similar doses in controlling hyperglycemia in type 2 diabetes. Secondary: Not reported
Hong et al. ³⁸	DB, MC, PC, RCT	N=304	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(SPREAD-DIMCAD) (2013)</p> <p>Metformin 0.75 to 1.5 grams daily</p> <p>vs</p> <p>glipizide 15 to 30 mg daily</p>	<p>Patients 80 years of age or below with coronary artery disease (CAD) and type 2 diabetes</p>	<p>3 years</p>	<p>Composite of recurrent cardiovascular events (myocardial infarction [MI], nonfatal stroke, arterial revascularization, death)</p> <p>Secondary: New or worsening angina, new or worsening heart failure, new critical cardiac arrhythmia, and new peripheral vascular events.</p>	<p>A total of 103 composite primary end points occurred in 91 during the whole study period: 60 events in the glipizide group (14 deaths from any causes [including 11 deaths from cardiovascular events and 3 from sudden death; autopsies were not performed to confirm the 3 patients' precise causes of death], 6 nonfatal myocardial infarctions, 15 nonfatal strokes, and 25 arterial revascularizations), as compared with 43 events in the metformin group (7 deaths from any causes [all were deaths from cardiovascular events], 5 nonfatal myocardial infarctions, 10 nonfatal strokes, and 21 arterial revascularizations). As compared with the patients treated with glipizide, the HR for the composite cardiovascular events for metformin treatment was 0.54 (95% CI 0.30 to 0.90; P=0.026) after adjustment for the duration of diabetes, duration of CAD, age, sex, and smoking history at baseline. No significant difference in the mortality rate between the two groups was found (P=0.55).</p> <p>Secondary: During the study drug administration, the following secondary end points occurred:</p> <ul style="list-style-type: none"> • new or worsening heart failure: 10 (6.8%) patients in the glipizide group and 9 (5.8%) patients in the metformin group (adjusted HR, 0.82; 95% CI, 0.31 to 2.13; P=0.677) • new critical cardiac arrhythmia: 27 (18.2%) patients in the glipizide group and 30 (19.2%) patients in the metformin group (HR, 1.01; CI, 0.60 to 1.72; P=0.958) • new or worsening angina: 71 (48%) patients in the glipizide group and 77 (49.4%) patients in the metformin group (HR, 1.07; CI, 0.77 to 1.48; P=0.696) • new peripheral vascular events: 6 (4.1%) patients in the glipizide group and 1 (0.6%) patient in the metformin group (HR, 0.13; CI, 0.02 to 1.08; P=0.059) <p>Furthermore, the two groups did not differ significantly with respect to the number of patients who reported one or more hypoglycemic attacks during study drug administration.</p>
<p>Scott et al.³⁹ (2007)</p> <p>Sitagliptin 5 mg</p>	<p>AC, DB, PC, RCT</p> <p>Type 2 diabetics 21 to 75 years of age,</p>	<p>N=743</p> <p>12 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, mean daily glucose, and</p>	<p>Primary: Sitagliptin (-0.38 to -0.77%) significantly decreased HbA_{1c} compared to placebo (P<0.001). Sitagliptin 50 mg achieved the greatest decrease. The placebo subtracted difference in HbA_{1c} of glipizide was -1.00%.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs sitagliptin 12.5 mg BID vs sitagliptin 25 mg BID vs sitagliptin 50 mg BID vs glipizide 5 to 20 mg daily vs placebo	inadequately controlled (HbA _{1c} 7.9%) with diet and exercise		body weight; adverse effects Secondary: Not reported	Sitagliptin significantly decreased FPG and mean daily glucose compared to placebo (P values not reported). There was no difference between sitagliptin and placebo with changes in body weight. Glipizide resulted in a modest weight gain compared to placebo (no P value reported). The incidence of hypoglycemia was highest with glipizide (17%) compared to placebo (2%) and sitagliptin (0 to 4%, not dose-dependent). Secondary: Not reported
Chan et al. ⁴⁰ (2008) <u>Phase I</u> Sitagliptin 25 to 50 mg once daily vs placebo <u>Phase II</u>	DB, PC, PG, RCT Patients ≥18 years of age with type 2 diabetes, baseline HbA _{1c} 6.5 to 10.0%, and renal insufficiency	N=91 54 weeks (Phase I was 12 weeks; Phase II was 42 weeks)	Primary: Safety and tolerability Secondary: Efficacy	Primary: Adverse events were similar among patients receiving sitagliptin and placebo/glipizide, including serious adverse events (30.8 and 38.5%, respectively), drug-related serious adverse events (1.5 and 0.0%, respectively), and adverse events leading to discontinuation. Incidences of adverse events by body systems and specific clinical adverse events were also similar between the sitagliptin and placebo/glipizide groups, with the exception of hypoglycemia and anemia. Hypoglycemia occurred in 4.6% of patients receiving sitagliptin and 23.1% of patients receiving placebo/glipizide. Anemia occurred in 3.1% of patients receiving sitagliptin and 15.4% of patients receiving placebo/glipizide.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Glipizide 2.5 to 20 mg daily and placebo</p> <p>vs</p> <p>sitagliptin 25 to 50 mg daily and placebo</p>				<p>There was a higher incidence of MI (4.6 and 0.0%) and heart failure (7.7 and 3.8%) in the sitagliptin group compared to the placebo/glipizide group, respectively. The number of patients experiencing cardiovascular events per 100 patient-years was similar between groups.</p> <p>There were six deaths (7.7%) in the sitagliptin group and one death (3.8%) in the placebo/glipizide group. This represents an overall mortality rate of 7.3 deaths per 100 patient-years, with 8.8 and 4.0 deaths per 100 patient-years in the sitagliptin and placebo/glipizide groups, respectively.</p> <p>No clinically meaningful differences were observed for laboratory safety measures, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine phosphokinase, uric acid, electrolytes, white blood cell count or absolute neutrophil count between groups.</p> <p>At week 54, the mean change from baseline in serum creatinine for patients with moderate renal insufficiency was -0.02 and 0.69 mg/dL in the sitagliptin and placebo/glipizide groups, respectively.</p> <p>At week 54, small (2 mm Hg) mean decreases in systolic, diastolic and mean arterial BPs were observed for patients on sitagliptin compared to those on placebo/glipizide.</p> <p>At week 54, there was a small mean decrease in body weight from baseline in the sitagliptin group (-0.9 kg) compared with no mean change in the placebo/glipizide group (0.0 kg).</p> <p>Secondary:</p> <p>At week 12, the mean change from baseline in HbA_{1c} was -0.6% (95% CI, -0.8 to -0.4) in the sitagliptin group compared with -0.2% (95% CI, -0.4 to 0.1) in the placebo group</p> <p>At week 12, the mean change from baseline in FPG was -25.5 mg/dL (95% CI, -38.2 to -12.8) with sitagliptin and -3.0 mg/dL (95% CI, -15.7 to 9.6) with placebo.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>At week 54, the mean and least squares mean change from baseline in HbA_{1c} with sitagliptin was -0.7% in the prespecified analysis and in the ANCOVA analysis. The mean and least squares mean changes from baseline were -1.0 and -0.8%, respectively in the placebo/glipizide group. Between-group testing for efficacy was not performed at the week 54 time point.</p> <p>At week 54, the mean percent changes in lipids were as follows for sitagliptin: TC (+4.3%; 95% CI, -1.5 to 10.1), LDL-C (+11.9%; 95% CI, 1.6 to 22.2), and non-HDL-C (+7.1%; -1.2 to 15.3), TG (-0.7%; 95% CI, -13 to 11.5), and HDL-C (+0.9%; 95% CI, -5.9 to 7.7). The mean percent changes in lipids in the placebo/glipizide group were as follows: TC (-0.2%; 95% CI, -10.5 to 10), LDL-C (3.3%; 95% CI, -8.6 to 15.2), non-HDL-C (-1.6%; 95% CI, -13.7 to 10.5), TG (+0.9%; 95% CI, -27.5 to 29.3), and HDL-C (+6.6%; 95% CI, -5 to 18.2).</p>
<p>Sami et al.⁴¹ (1996)</p> <p>Glyburide 20 mg daily in two divided doses</p> <p>vs</p> <p>glipizide 40 mg daily in two divided doses</p>	<p>RCT</p> <p>Patients 43 to 73 years of age with non-insulin-dependent (type 2) diabetes mellitus for 5 to 15 years who manifested secondary failure to a first generation sulfonylurea (19 patients on chlorpropamide and 36 patients on tolazamide) while attending a diabetes clinic were randomly changed, at the discretion of the caring physician at the clinic</p>	<p>N=55</p> <p>6 months</p>	<p>Primary: Changes in body weight, FPG, HbA_{1c}, serum lipid profiles</p> <p>Secondary: Not reported</p>	<p>Primary: Body weight, FPG, HbA_{1c} levels, and lipid profiles were not significantly changed following the change over from the first generation agents (chlorpropamide and tolazamide) to second generation agents (glyburide and glipizide) in all patients, irrespective of the specific first and second generation agents given. Additionally, these values were not significantly changed when the patients were divided into two groups according to the second generation agent used.</p> <p>There were no significant changes (P<0.5) in the levels of FBG and HbA_{1c} in the patients following the change over to glipizide. FPG was 211±34 mg/L and HbA_{1c} was 11.7±1.8% compared to 209±31 mg/L and 12.3±2.1% respectively, obtained following treatment with the first generation agents (chlorpropamide and tolazamide).</p> <p>There were no significant changes (P>0.5) observed in the patients changed over to glyburide. FPG was 184±20 mg/dL and HbA_{1c} was 11.0±1.4% following the change over from the first generation agents (chlorpropamide and tolazamide). Prior to the change over, FPG was 180±16 mg/dL and HbA_{1c} was 11.2±1.6%.</p> <p>Lipid concentrations were not significantly changed in either groups</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>following the change over to glyburide or glipizide when compared to prior treatment with the first generation agents.</p> <p>There were no significant changes in the metabolic values when the glyburide and glipizide groups were further subdivided according to the specific first generation agent used.</p> <p>Secondary: Not reported</p>
<p>Hollander et al.⁴² (2003)</p> <p>Nateglinide 120 mg TID before each meal</p> <p>vs</p> <p>glyburide 5 to 10 mg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients 32 to 75 years of age with type 2 diabetes ≥ 3 months prior to entry into the trial on diet modification alone for ≥ 4 weeks before initial visit, mean HbA_{1c} 6.8 to 11.0%, and a BMI 20 to 35 kg/m²</p>	<p>N=152</p> <p>8 weeks</p>	<p>Primary: Change from week 0 to week eight during liquid meal challenges in FPG, fasting insulin, fasting C-peptide, and fasting proinsulin</p> <p>Secondary: Not reported</p>	<p>Primary: At week eight, FPG was reduced more with glyburide compared to nateglinide (-1.9 mmol/L; P<0.001).</p> <p>Nateglinide treatment did not have significant changes from baseline with fasting levels of C-peptide, insulin, or proinsulin.</p> <p>Glyburide treatment increased fasting C-peptide vs placebo and nateglinide (P<0.001), fasting insulin vs placebo (P<0.001) and nateglinide (P<0.05), and proinsulin vs placebo (P<0.001) and nateglinide (P<0.025).</p> <p>Reduction of mealtime glucose excursions from nateglinide was approximately twice that from glyburide (-4.94\pm0.74 vs -2.71\pm0.71 mmol/hr/L; P<0.03).</p> <p>The insulin secretion reflected by the C-peptide AUCs was approximately twice that in the glyburide group than in the nateglinide group (1.83\pm0.24 vs 0.95\pm0.23 nmol/hr/L, respectively; P=0.063 vs nateglinide).</p> <p>Secondary: Not reported</p>
<p>Kahn et al.⁴³ (2006)</p> <p>Glyburide 2.5 to 7.5 mg BID</p>	<p>DB, MC, RCT</p> <p>Recently diagnosed (within 3 years) type 2 diabetic patients between the</p>	<p>N=4,360</p> <p>4 to 6 years (median treatment durations 3.3</p>	<p>Primary: Time from randomization to treatment failure (defined as FPG >180 mg/dL on</p>	<p>Primary: At five years, 15% of patients receiving rosiglitazone, 21% of those on metformin, and 34% of those on glyburide had failed monotherapy. This represents a risk reduction of 32% for rosiglitazone as compared with metformin and 63% for rosiglitazone as compared with glyburide (P<0.001 for both comparisons).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>metformin 500 to 1,000 mg BID</p> <p>vs</p> <p>rosiglitazone 4 mg QD to 4 mg BID</p>	<p>ages of 30 to 75 years who had not received previous pharmacologic treatment, with FPG levels ranging from 126 to 180 mg/dL while their only treatment was lifestyle management</p>	<p>years for glyburide and 4 years for rosiglitazone and metformin)</p>	<p>consecutive testing after at least six weeks of treatment at the maximum tolerated dose)</p> <p>Secondary: Time from randomization to a confirmed FPG >140 mg/dL after at least six weeks of treatment at the maximum tolerated dose (for patients who entered the study with FPG ≤140 mg/dL); also FPG, HbA_{1c}, weight, measures of insulin sensitivity, β-cell function, and adverse events</p>	<p>Secondary: Progression to a confirmed FPG ≥140 mg/dL was seen in 79 of 511 patients in the rosiglitazone group as compared with 127 of 520 patients in the metformin group (P=0.002) and 160 of 480 patients in the glyburide group (P<0.001).</p> <p>At the 4-year evaluation, 40% of the patients in the rosiglitazone group achieved an HbA_{1c} <7.0% compared with 36% of the patients in the metformin group (P=0.03) and 26% of the patients in the glyburide group (P<0.001).</p> <p>The annual rate of β-cell function decline after 6 months was greatest in the glyburide group (6.1% decreased), followed by the metformin group (3.1% decreased) and rosiglitazone group (2.0% decreased) (P<0.001 for rosiglitazone vs glyburide and P=0.02 for rosiglitazone vs metformin).</p> <p>Over a period of five years, the mean weight increased in the rosiglitazone group but decreased in the metformin group. In the glyburide group, weight gain occurred in the first year then remained stable.</p> <p>Treatment with glyburide group was associated with lower risk of cardiovascular events (including congestive heart failure) than was seen in the rosiglitazone and metformin groups (P<0.05). Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide, but fewer gastrointestinal events were reported with rosiglitazone compared to metformin and fewer hypoglycemic events were seen with rosiglitazone compared to with glyburide (P<0.001 for all comparisons).</p>
<p>Giles et al.⁴⁴ (2008)</p> <p>Glyburide 10 to 15 mg daily</p> <p>vs</p> <p>pioglitazone 30 to</p>	<p>DB, MC, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes, HbA_{1c} ≥7.0%, BMI ≤48 kg/m², NYHA functional Class II/III heart failure,</p>	<p>N=518</p> <p>6 months</p>	<p>Primary: Heart failure progression (defined as the composite of cardiovascular mortality and hospitalization or emergency room</p>	<p>Primary: Pioglitazone was associated with a higher incidence rate of the composite end point compared with glyburide (13.4 vs 8.2%, respectively; P=0.024).</p> <p>Death from cardiovascular cause was similar between the treatment groups (1.9 and 2.3% for pioglitazone and glyburide, respectively).</p> <p>Overnight hospitalization for heart failure was higher in the pioglitazone group (9.9%) compared to glyburide group (4.7%).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>45 mg QD</p> <p>Insulin was the only rescue medication allowed.</p>	<p>left ventricular systolic dysfunction ($\leq 40\%$), and receiving sulfonylurea therapy (+/- insulin) for ≥ 30 days before screening or discontinued metformin therapy within 30 days of screening</p>		<p>visit for heart failure) and metabolic parameters.</p> <p>Secondary: Not reported</p>	<p>Emergency room visits for heart failure occurred in 1.5% of pioglitazone patients compared to 1.2% of glyburide patients.</p> <p>Echocardiographic data demonstrated preserved cardiac function with similar changes in the left ventricular mass index ($P=0.959$) and left ventricular ejection fraction ($P=0.413$) among the treatment groups. Cardiac index was significantly increased with pioglitazone compared with glyburide ($P=0.012$).</p> <p>FPG was significantly decreased with glyburide relative to pioglitazone during the first 4 weeks of treatment. By week 16, a significant difference in mean FPG was observed favoring pioglitazone. At week 24, pioglitazone decreased the HbA_{1c} by -0.98% compared to -0.73% with glyburide ($P=0.007$).</p> <p>At week 24, significant differences were seen between pioglitazone and glyburide in TGs (-36.8 vs +7.6 mg/dL, respectively; $P<0.001$), HDL-C (+4.8 vs -0.8 mg/dL, respectively; $P<.001$), and LDL-C (+6.9 vs -2.4 mg/dL, respectively; $P<0.016$).</p> <p>Rates of adverse events and serious adverse events were similar between treatment groups. Hypoglycemia was more common with glyburide and edema was more common with pioglitazone. Weight gain was reported as an adverse event more frequently with pioglitazone than glyburide. (6.1 vs 2.7%, respectively). Mean weight gain was greater (2.10 vs 1.23 kg, respectively; $P=0.012$) with pioglitazone than with glyburide.</p> <p>Secondary: Not reported</p>
<p>Johnston et al.⁴⁵ (1998)</p> <p>Glyburide 1.25 to 20 mg QD</p> <p>vs</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥ 60 years of age with type 2 diabetes treated with diet alone for</p>	<p>N=411</p> <p>1 year</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline plasma glucose,</p>	<p>Primary: Mean placebo-subtracted HbA_{1c} reduction from baseline was -0.50% with miglitol 25 mg TID ($P<0.05$ vs glyburide), -0.41% with miglitol 50 mg TID ($P<0.05$ vs glyburide), -0.93% for glyburide QD, and -0.01% for placebo ($P<0.05$ vs all active treatments).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
miglitol 25 to 50 mg TID vs placebo	≥12 weeks, HbA _{1c} 6.5 to 10.0%, and FPG >140 mg/dL		serum insulin, and TG	<p>Changes in mean plasma glucose (AUC) were +716 mg·min/dL with placebo (P<0.05 vs all active treatments), -3,361 mg·min/dL with miglitol 25 mg TID, -5,462 mg·min/dL with miglitol 50 mg TID, and -3,615 mg·min/dL with glyburide (P=0.0001 for miglitol 50 mg TID vs placebo).</p> <p>Postprandial insulin levels were significantly greater with glyburide compared to placebo and miglitol (P<0.01).</p> <p>Mean changes from baseline to end point for fasting TG were 1.01 with placebo and miglitol 25 mg TID, 0.98 with miglitol 50 mg TID, and one with glyburide (P=0.573 for miglitol 50 mg vs placebo).</p> <p>Mean changes from baseline to end point for TG (AUC) were 1.01 with placebo, 1.03 with miglitol 25 mg TID, 1.00 with miglitol 50 mg TID, and 1.06 with glyburide (P=0.8559 miglitol 50 mg TID vs placebo).</p> <p>Hypoglycemia, weight gain, and routine and serious cardiovascular events were more frequent in the glyburide group (P<0.05 vs placebo and miglitol).</p>
van de Laar et al. ⁴⁶ (2004) Tolbutamide titrated 2,000 mg daily in 3 divided doses vs acarbose titrated to 100 mg TID	DB, RCT Newly diagnosed patients with type 2 diabetes 40 to 70 years of age and a FPG level 6.7 to 20 mmol/L after an 8-week dietary treatment period	N=96 30 weeks	Primary: Change in HbA _{1c} from baseline Secondary: Change in fasting and post-load blood glucose and insulin levels, plasma lipids, and tolerability	<p>Primary: Both treatment groups showed a decrease in HbA_{1c}. The HbA_{1c} change from baseline for the acarbose group was -1.1 vs -1.8% for the tolbutamide group. The difference between the groups was 0.6% in favor of tolbutamide (90% CI, 0.3 to 0.9 and 95% CI, 0.2 to 1.0).</p> <p>Secondary: Difference in mean decrease of FPG was 1.0 mmol/L in favor of tolbutamide (95% CI, 0.3 to 1.7).</p> <p>No significant differences were seen in post-load blood glucose, fasting and post-load insulin levels, or lipids.</p> <p>Significantly more patients in the acarbose group (15 vs 3) discontinued therapy because of adverse effects, mostly gastrointestinal.</p>
Sullivan et al. ⁴⁷ (2011) FIELD	PRO Patients with type 2 diabetes	N=6,005 5 years	Primary: Cardiovascular disease outcomes	Primary: Patients receiving monotherapy with either metformin or a sulfonylurea appeared to be at greater risk of cardiovascular disease compared to those on diet alone, but results were only significant for the sulfonylurea group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metformin vs sulfonylurea vs diet alone			Secondary: Hypoglycemic therapy	ranging from 42% higher risk of coronary revascularization to a doubled risk of coronary heart disease death. However, adjustment for the duration and intensity of diabetes and the severity of other cardiovascular risk factors abolished the significance of this effect. Total revascularization and total mortality were significantly higher in the sulfonylurea group compared to the metformin group, but all differences became non-significant on adjustment. Secondary: Use of oral hypoglycemic agents increased progressively as the trial proceeded. Over five years, treatment with diet alone decreased from 31 to 15%, and dual therapy with metformin plus a sulfonylurea increased from 29 to 36%. Insulin therapy was introduced at a rate of 4% per year. Metformin monotherapy declined from 21 to 18% but the sulfonylurea monotherapy rate declined from 20 to 12%. Patients on sulfonylurea monotherapy were more likely to progress to dual therapy.
Simpson et al. ⁴⁸ (2006) First-generation sulfonylurea vs glyburide vs metformin	RETRO New users of one oral diabetic agent	N=5,95 ~4.6 years	Primary: Mortality Secondary: Not reported	Primary: An increased risk of death was associated with higher daily doses of first-generation sulfonylureas (adjusted HR, 2.1; 95% CI, 1.0 to 4.7) and glyburide (HR, 1.3; 95% CI, 1.2 to 1.4) compared to metformin (HR, 0.8; 95% CI, 0.7 to 1.1). Secondary: Not reported
Nichols et al. ⁴⁹ (2007) Metformin vs sulfonylurea	MC, OS, RETRO Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of	N=9,546 ≥12 months	Primary: Weight changes Secondary: Not reported	Primary: Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin vs TZDs	that drug for at least 12 months without adding other therapies			
Gangji et al. ⁵⁰ (2001) Glyburide vs sulfonylureas, meglitinides, insulin	MA (21 trials) Patients with type 2 diabetes	N=not reported Duration varied	Primary: Hypoglycemia, glycemic control, cardiovascular events, body weight, death Secondary: Not reported	Primary: Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52; 95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49). Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues. Secondary: Not reported
Bolen et al. ⁵¹ (2007) Biguanides vs meglitinides vs TZDs vs α -glucosidase inhibitors	MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs) Patients with type 2 diabetes	N=136 (articles on intermediate outcomes) N=167 (articles on adverse events) N=68 (articles on micro-vascular outcomes and mortality)	Primary: Intermediate outcomes: HbA _{1c} , body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes Secondary: Adverse events: hypoglycemia, gastrointestinal problems,	Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA _{1c} level of about 1%). Nateglinide and α -glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials. TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C. TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP. Most agents except metformin increased body weight by 1 to 5 kg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs second-generation sulfonylureas		Duration varied	congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events	<p>In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05).</p> <p>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).</p> <p>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.</p> <p>Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).</p> <p>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.</p> <p>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.</p> <p>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.</p>
Monami et al. ⁵² (2008) Metformin	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable	Primary: Reduction in HbA _{1c} at 16 to 36 months	Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α -glucosidase inhibitors, and TZDs led to a reduction in HbA _{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sulfonylureas, α -glucosidase inhibitors, TZDs, glinides, GLP-1 agonists		duration	Secondary: Not reported	0.40 to 0.44), respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA _{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α -glucosidase inhibitors, and between α -glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported
Saenz et al. ⁵³ (2005) Metformin monotherapy vs placebo, sulfonylureas, TZDs, meglitinides, α - glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin	MA (29 RCTs) Adult patients with type 2 diabetes	N=5,259 ≥ 3 months	Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photo- coagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo- glycemia or	Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03). Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02). Secondary: Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA _{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>hyperglycemia, and sudden death); all-cause mortality</p> <p>Secondary: Changes in HbA_{1c}, FPG, QOL, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow</p>	
<p>Shyangdan et al.⁵⁴ (2011)</p> <p>GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)</p> <p>vs</p> <p>non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)</p>	<p>MA (RCTs)</p> <p>Type 2 diabetics ≥18 years of age</p>	<p>N=not reported</p> <p>8 to 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change</p> <p>Secondary: Health-related QOL, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function</p>	<p>Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).</p> <p>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78).</p> <p>Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).</p> <p>Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).</p> <p>Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92).</p> <p>Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).</p> <p>Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).</p> <p>Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).</p> <p>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).</p> <p>Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).</p> <p>Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Secondary: Data on mortality and morbidity were not reported for any treatment.</p> <p>QOL Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.</p> <p>Data for liraglutide were not reported.</p> <p>Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).</p> <p>Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.</p> <p>BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>reported.</p> <p>Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported.</p> <p>FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).</p> <p>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported).</p> <p>PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).</p> <p>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable.</p> <p>Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.</p> <p>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported.</p> <p>β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.</p>
<p>Frederich et al.⁵⁵ (2010)</p> <p>Saxagliptin 2.5 to 10 mg QD</p> <p>vs</p> <p>glyburide, metformin, or placebo</p>	<p>SR (RCTs)</p> <p>Inadequately controlled type 2 diabetics</p>	<p>N=4,607</p> <p>16 to 116 weeks</p>	<p>Primary: Composite of cardiovascular events, cardiovascular death, MI, and stroke</p> <p>Secondary: Not reported</p>	<p>Primary: There were 38 (1.1%) cardiovascular events with saxagliptin compared to 23 (1.8%) with the comparator drugs (RR, 0.59; 95% CI, 0.35 to 1.00). There were 23 (0.7%) cardiovascular deaths, MIs, and stroke events with saxagliptin compared to 18 (1.4%) with the comparator drugs (RR, 0.44; 95% CI, 0.24 to 0.82). There were seven (0.2%) cardiovascular deaths with saxagliptin compared to 10 (0.8%) with comparator drugs (RR, 0.24; 95% CI, 0.09 to 0.63).</p> <p>Secondary: Not reported</p>
<p>Singh et al.⁵⁶ (2011)</p> <p>TZDs (pioglitazone,</p>	<p>MA, SR (13 RCTs)</p> <p>Type 2 diabetics</p>	<p>N=17,627</p> <p>1 to 5.5 years (follow-up)</p>	<p>Primary: Any pneumonia or lower respiratory tract infection reported as an</p>	<p>Primary: TZDs are associated with a significantly increased risk for any pneumonia or lower respiratory tract infection compared to control (130/8,163 vs 100/9,464; RR, 1.40; 95% CI, 1.08 to 1.82; P=0.01). In addition TZDs were associated with a significantly increased risk of serious pneumonia or lower</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone) vs placebo, sulfonylurea, or metformin			adverse event, pneumonia or lower respiratory tract infection reported as a serious adverse event Secondary: Not reported	respiratory tract infection compared to control (111/7,391 vs 87/8,692; RR, 1.39; 95% CI, 1.05 to 1.83; P=0.02). Secondary: Not reported
Louisa et al. ⁵⁷ (2011) TZDs (pioglitazone, rosiglitazone) vs placebo or other hypoglycemic agents	MA (37 RCTs) Type 2 diabetics	N=3,000 >3 months	Primary: Glycemic outcomes Secondary: Change in baseline BMI, lipid profile, BP, high- sensitivity CRP, and insulin sensitizing effect; cardiovascular and clinical endpoints	Primary: Both pioglitazone (WMD, -0.12%; 95% CI, -0.38 to -0.16) and rosiglitazone (WMD, -0.47%; 95% CI, -0.62 to -0.33) significantly decreased HbA _{1c} . Pioglitazone only demonstrated a significant decrease compared to placebo, while rosiglitazone significantly decreased HbA _{1c} compared to placebo and a sulfonylurea. Both pioglitazone (WMD, -9.16 mg/dL; 95% CI, -15.60 to -2.72) and rosiglitazone (WMD, -16.10 mg/dL; 95% CI, -22.20 to -10.01) significantly decreased FPG compared to control. Pioglitazone demonstrated a significant decrease compared to placebo, metformin, and voglibose†, while rosiglitazone significantly decreased FPG compared to placebo, metformin, and a sulfonylurea. Secondary: Pioglitazone and rosiglitazone had similar effects on BMI (pioglitazone: WMD, 0.57; 95% CI, 0.34 to 0.80 and rosiglitazone: WMD, 0.72; 95% CI, 0.29 to 1.14). Pioglitazone demonstrated a neutral effect of LDL-C (WMD, 3.89 mg/dL; 95% CI, -0.04 to 7.83) and TC (WMD, 2.30 mg/dL; 95% CI, -3.81 to 8.41). Rosiglitazone significantly increased LDL-C (WMD, 11.30 mg/dL; 95% CI, 7.80 to 14.79) and TC (WMD, 7.34 mg/dL; 95% CI, 2.34 to 12.31). Both agents had favorable effects on HDL-C and TGs. Pioglitazone produced a small decrease in DBP and SBP, while

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>rosiglitazone demonstrated a neutral effect.</p> <p>In 13 trials, pioglitazone demonstrated a neutral effect on high sensitivity CRP, while rosiglitazone demonstrated a small improvement in hsCRP.</p> <p>Consistent increase in adiponectin and improvement in HOMA-IR were observed with both pioglitazone and rosiglitazone.</p> <p>Four trials evaluated cardiovascular events as secondary endpoints. There were significant decreases in major cardiac events with both pioglitazone vs control (RR, 0.24; 95% CI, 0.09 to 0.63) and rosiglitazone vs control (RR, 0.41; 95% CI, 0.19 to 0.87).</p>
<p>Mannucci et al.⁵⁸ (2008)</p> <p>Pioglitazone</p> <p>vs</p> <p>active comparators, placebo, no treatment</p>	<p>MA (94 trials)</p> <p>Patients treated with pioglitazone (with or without type 2 diabetes)</p>	<p>N=21,180</p> <p>Variable duration</p>	<p>Primary: All-cause mortality, non-fatal coronary event (defined as MI, unstable angina or coronary re-vascularization), non-fatal chronic heart failure requiring hospitalization</p> <p>Secondary: Not reported</p>	<p>Primary: In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality (P value not reported).</p> <p>In non-diabetic patients, only one death was observed occurring among pioglitazone-treated patients.</p> <p>In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR, 0.41; 95% CI, 0.23 to 0.72).</p> <p>When analyzing all trials, no significant reduction of mortality was observed with pioglitazone.</p> <p>Comparing different agents, pioglitazone was associated with a lower mortality rate compared to sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars, or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR, 0.22; 95% CI, 0.05 to 1.03), metformin (RR, 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR, 0.49; 95% CI, 0.04 to 5.36), glitazars (RR, 0.42; 95% CI, 0.11 to 1.61), or placebo (RR, 0.16; 95% CI, 0.02 to 1.45).</p> <p>In PROactive, pioglitazone significantly reduced the incidence of non-fatal coronary events (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported.</p> <p>In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR, 0.82; 95% CI, 0.55 to 1.23).</p> <p>Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant.</p> <p>In PROactive, pioglitazone was associated with an increased risk for chronic heart failure. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR ,1.32; 95% CI, 0.88 to 1.98).</p> <p>Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not significant (P value not reported). When adding PROactive or excluding trials vs dual PPARα/γ agonists pioglitazone was associated with a significant increase of risk for chronic heart failure.</p> <p>In comparison with different agents, pioglitazone was associated with an increased risk of chronic heart failure in PC trials, while differences with sulfonylureas or glitazars did not reach significance.</p> <p>Secondary: Not reported</p>
<p>Richter et al.⁵⁹ (2006)</p> <p>Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials),</p>	<p>MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG</p> <p>Adults with type 2 diabetes, trial</p>	<p>22 trials</p> <p>N=6,200 randomized to pioglitazone treatment (total N not reported)</p>	<p>Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects</p> <p>Secondary:</p>	<p>Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095).</p> <p>Time to the first event of the composite end point of death from any cause,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials)</p> <p>or</p> <p>pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone)</p> <p>Some studies had more than one treatment arm.</p>	<p>duration of at least 24 weeks</p>	<p>24 weeks to 34.5 months</p>	<p>Health-related QOL and HbA_{1c}</p>	<p>MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).</p> <p>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and -0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 kg/m². Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled.</p> <p>Secondary: No study investigated health-related QOL.</p> <p>Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (P values not reported).</p>
<p>Lago et al.⁶⁰ (2007)</p> <p>Pioglitazone 15 to 45 mg/day (2 trials) or rosiglitazone 4 to 8 mg/day (5 trials)</p> <p>vs</p>	<p>MA of DB, RCTs of TZDs that reported risk estimates or frequency data for congestive heart failure and cardiovascular death</p> <p>Patients with</p>	<p>7 trials</p> <p>N=20,191</p> <p>29.7 months (range, 12 to 48 months)</p>	<p>Primary: Development of congestive heart failure, risk of cardiovascular death</p> <p>Secondary: Not reported</p>	<p>Primary: Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). The overall event rate for congestive heart failure was 2.3% for patients receiving TZDs and 1.4% in the comparator group.</p> <p>Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of congestive heart failure across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95% CI,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo (4 trials), glibenclamide‡ (1 trial), glimepiride (1 trial), metformin (1 trial), or metformin plus nonspecified sulfonylurea (1 trial)</p> <p>Doses of comparators were not specified and 1 trial had 2 control groups.</p>	<p>prediabetes or type 2 diabetes (with and without cardiovascular disease), mean age 59.2 years, mean BMI 31 kg/m², mean baseline HbA_{1c} 7.72%</p>			<p>1.21 to 2.42; P=0.002). The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07).</p> <p>The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI, 0.63 to 1.32; P=0.63) or both TZDs (combined RR, 0.93; 95% CI, 0.67 to 1.29; P=0.68). The risk of cardiovascular death did not differ between both drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96).</p> <p>Secondary: Not reported</p>
<p>Nagajothi et al.⁶¹ (2008)</p> <p>Pioglitazone vs active comparators (metformin and/or sulfonylurea) or placebo</p>	<p>MA (5 trials)</p> <p>Patients treated with pioglitazone</p>	<p>N=not reported</p> <p>Duration varied</p>	<p>Primary: MI</p> <p>Secondary: Stroke, revascularization, total mortality, cardiovascular mortality</p>	<p>Primary: The RR for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17).</p> <p>Secondary: The RR for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07).</p> <p>The RR for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56).</p> <p>The RR for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11).</p> <p>The RR for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47).</p>
<p>Lincoff et al.⁶² (2007)</p> <p>Pioglitazone monotherapy vs metformin (1 trial), placebo (4 trials), sulfonylureas (6</p>	<p>DB, MA, RCT with placebo or active comparator</p> <p>Adult patients with type 2 diabetes and inadequate glycemic control</p>	<p>N=16,390 (19 trials)</p> <p>4 months to 3.5 years</p>	<p>Primary: Composite of death from any cause, MI or stroke</p> <p>Secondary: Incidence of serious heart</p>	<p>Primary: Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005).</p> <p>Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85;</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>trials) or rosiglitazone (1 trial)</p> <p>or</p> <p>pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo</p>			<p>failure</p>	<p>P=0.04, and stroke: HR, 0.80; P=0.09).</p> <p>Progressive separation of time-to-event curves became apparent after approximately one year of therapy.</p> <p>Secondary: Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).</p>
<p>Karter et al.⁶³ (2005)</p> <p>Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies</p>	<p>Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001</p>	<p>N=23,440</p> <p>10.2 months (mean)</p>	<p>Primary: Time-to-incident admission to hospital for congestive heart failure</p> <p>Secondary: Not reported</p>	<p>Primary: Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99).</p> <p>Secondary: Not reported</p>
<p>Nissen et al.⁶⁴ (2007)</p> <p>Rosiglitazone monotherapy or combination therapy</p>	<p>MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and</p>	<p>42 trials</p> <p>n=15,560 for rosiglitazone ; n=12,283 for comparator</p>	<p>Primary: MI and death from cardiovascular causes</p> <p>Secondary: Not reported</p>	<p>Primary: Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03).</p> <p>Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo or active comparators (including gliclazide†, glimepiride, glipizide, glyburide, insulin, and metformin)	DREAM trials) Mean age of participants was 56 years, mean baseline HbA _{1c} 8.2%	24 to 208 weeks		Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24). Secondary: Not reported
Singh et al. ⁶⁵ (2007) Rosiglitazone vs control (placebo or other non-TZD oral hypoglycemic drug including glyburide or metformin)	MA of RCTs (available up to May 2007 and included ADOPT, DREAM and RECORD trials) of rosiglitazone of at least 12 months duration Study participants with impaired glucose tolerance or type 2 diabetes, studies monitored cardiovascular adverse events and provided numerical data on all adverse events	4 trials N=14,291 (n=6,421 rosiglitazone ; n=7,870 control) 1 to 4 years	Primary: RR of MI, heart failure, and cardiovascular mortality Secondary: Not reported	Primary: Rosiglitazone significantly increased the risk of MI (94 vs 83; RR, 1.42; 95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control. There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53). Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; 95% CI, 0.80 to 1.23; P=0.92). Secondary: Not reported
Richter et al. ⁶⁶ (2007) Rosiglitazone monotherapy (10 trials) vs glyburide (2 trials),	MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG	18 trials N=3,888 randomized to rosiglitazone treatment	Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects	Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial)</p> <p>or</p> <p>rosiglitazone combination therapy vs a similar combination with another compound (8 trials)</p> <p>Some studies had more than 1 treatment arm.</p>	<p>Adults with type 2 diabetes, trial duration of at least 24 weeks</p>	<p>(total N not reported)</p> <p>24 weeks to 4 years (median 26 weeks)</p>	<p>Secondary: Health-related QOL and metabolic control (HbA_{1c})</p>	<p>The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference).</p> <p>The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in BMI up to 1.5 kg/m². Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01).</p> <p>Secondary: No study investigated health-related QOL.</p> <p>Active glucose-lowering compounds like metformin, glibenclamide‡ or glimepiride resulted in similar reductions of HbA_{1c} compared to</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rosiglitazone treatment.
Type 2 Diabetes – Combination Therapy				
<p>Lopez-Alvarenga et al.⁶⁷ (1999)</p> <p>Chlorpropamide 500 mg daily, metformin 1,200 mg daily, and acarbose 100 mg TID</p> <p>vs</p> <p>chlorpropamide 500 mg daily, metformin 1,200 mg daily, and NPH insulin at bedtime</p> <p>vs</p> <p>chlorpropamide 500 mg daily, metformin 1,200 mg daily, and placebo</p>	<p>DB, RCT, XO</p> <p>Patients with type 2 diabetes 35 to 70 years of age with BMI 23 to 35 kg/m², with a fasting plasma glucose above 8.8 mmol/L despite maximal doses of chlorpropamide and metformin for at least 2 months</p>	<p>N=46</p> <p>42 weeks</p>	<p>Primary: Change in FPG from baseline, body weight, HbA_{1c}, fasting insulin, fasting C-peptide, intravenous glucose tolerance test (incremental area), glucose meal tests (incremental area)</p> <p>Secondary: Not reported</p>	<p>Primary: Changes in FPG from baseline were not significant for placebo (P=0.62), but were significant for acarbose (P=0.05) and insulin (P=0.003).</p> <p>Changes in HbA_{1c} from baseline were not significant for placebo (P=0.62) and acarbose (P=0.3), but were significant for insulin (P=0.008).</p> <p>Changes in body weight were not significant in any group; P=0.2 for each group from baseline.</p> <p>Changes in fasting insulin from baseline were not significant for placebo (P=0.38), but were significant for acarbose (P=0.03) and insulin (P=0.02).</p> <p>Changes in fasting C-peptide from baseline were not significant in any group, placebo (P=0.7), acarbose (P=0.5), and insulin (P=0.24).</p> <p>Changes in intravenous glucose tolerance test (incremental area) from baseline were not significant in any group, placebo (P=0.36), acarbose (P=0.91), and insulin (P=0.94).</p> <p>Changes in glucose meal tests (incremental area) from baseline were not significant for placebo (P=0.84) and insulin (P=0.08), but were for acarbose (P=0.02).</p> <p>Changes in insulin (incremental area) from baseline were not significant for any group, placebo (P=0.92), acarbose (P=0.3), and insulin (P=0.43).</p> <p>Thirty-seven percent of patients developed severe bloating during acarbose use. This was significant (P<0.05) compared to acarbose and placebo or insulin.</p> <p>Secondary: Not reported</p>
<p>Yokoyama et al.⁶⁸ (2011)</p>	<p>OL, XO</p>	<p>N=25</p>	<p>Primary: Plasma glucose</p>	<p>Primary: During meal tolerance tests performed at the end of each three month period,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Continuation of glimepiride for 3 months</p> <p>vs</p> <p>discontinuation of glimepiride for 3 months</p> <p>All patients received metformin and basal insulin.</p>	<p>Patients with type 2 diabetes ≥ 5 years duration who are receiving insulin, metformin, and a sulfonylurea; BMI ≤ 40 kg/m², and HbA_{1c} $\leq 8.0\%$</p>	<p>6 months</p>	<p>levels, change in baseline HbA_{1c}</p> <p>Secondary: Not reported</p>	<p>significant increases in plasma glucose were seen in patients who discontinued glimepiride at 0-, 30-, and 60-minutes, while significant decreases in serum C-peptide were observed as 60- and 120-minutes.</p> <p>HbA_{1c} significantly increased in patients discontinuing glimepiride (from 6.6\pm0.6 at baseline to 7.7\pm0.8 at three months; P<0.0001). Increases in HbA_{1c} were closely correlated with decreases in AUC of meal-stimulated serum C-peptide (P<0.001).</p> <p>Secondary: Not reported</p>
<p>Dhindsa et al.⁶⁹ (2003)</p> <p>Glimepiride 2 mg QD</p> <p>vs</p> <p>gliclazide† 80 mg BID</p> <p>All patients received existing metformin regimens.</p>	<p>DB, RCT, XO</p> <p>Patients 50 to 70 years of age with type 2 diabetes and inadequate glycemic control despite metformin 500 mg BID monotherapy</p>	<p>N=12</p> <p>12 weeks</p>	<p>Primary: Changes in fructosamine, augmentation index, peak microvascular response to acetylcholine and sodium nitroprusside, and PD₁₀ values (dose of agonist required to increase mean arterial BP by 10 mm Hg)</p> <p>Secondary: Not reported</p>	<p>Primary: Metabolic control improved following the addition of a sulfonylurea, as seen by the reductions in serum fructosamine concentrations, but there were no significant differences in the antidiabetic effect between glimepiride and gliclazide as add-on therapy.</p> <p>There was no change in augmentation index during treatment with either sulfonylurea.</p> <p>There were no differences in pressor responsiveness (PD₁₀) or microvascular responses between the two treatment groups.</p> <p>Secondary: Not reported</p>
<p>Cefalu et al.⁷⁰ CANTATA-SU (2013)</p>	<p>AC, DB, NI, RCT</p> <p>Patients aged 18 to 80 years with type 2</p>	<p>N=1,450</p> <p>52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p>	<p>Primary: Both canagliflozin doses were non-inferior to glimepiride for lowering of HbA_{1c}, and canagliflozin 300 mg was superior to glimepiride for HbA_{1c} reduction. The least squares mean change from baseline was -0.81, -0.82,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Canagliflozin 100 mg vs canagliflozin 300 mg vs glimepiride titrated to a maximum of 6 or 8 mg/day</p>	<p>diabetes and an HbA_{1c} between 7.0 and 9.5% receiving stable metformin therapy</p>		<p>Secondary: Percentage change from baseline in bodyweight, proportion of patients with documented hypoglycemic episodes</p>	<p>and -0.93% in the glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.</p> <p>Secondary: The proportion of patients with documented hypoglycemic episodes was significantly lower with canagliflozin 100 mg and 300 mg than with glimepiride ($P<0.0001$ for both). The frequency of severe hypoglycemia was also lower with canagliflozin 100 mg (two [$<1\%$] patients) and 300 mg (three [$<1\%$]) than with glimepiride (15 [3%]).</p> <p>Both canagliflozin doses significantly reduced bodyweight at week 52, whereas a slight increase occurred with glimepiride ($P<0.0001$ for both canagliflozin doses vs glimepiride).</p>
<p>Derosa et al.⁷¹ (2011) Exenatide 5 µg SC BID, titrated up to 10 µg SC BID vs glimepiride 1 mg TID, titrated up to 2 mg TID</p>	<p>MC, RCT, SB Patients ≥ 18 years of age with type 2 diabetes intolerant to metformin at the highest dosages (2,500 to 3,000 mg/day)</p>	<p>N=111 12 months</p>	<p>Primary: Change in baseline body weight, glycemic control, insulin resistance</p> <p>Secondary: Not reported</p>	<p>Primary: There was decrease of body weight and BMI after six, nine, and 12 months ($P<0.05$, $P<0.01$, $P<0.001$, respectively) with exenatide, not obtained with glimepiride. BMI reached with exenatide was significantly lower compared to glimepiride ($P<0.05$).</p> <p>A similar decrease in HbA_{1c}, FPG, and PPG after nine ($P<0.05$ for all), and after 12 months ($P<0.01$ for all) with both treatments, without significant differences between the two treatments.</p> <p>Exenatide resulted in a reduction of fasting plasma insulin, and HOMA-IR after 12 months ($P<0.05$ for both), not observed with glimepiride; fasting plasma insulin increased with glimepiride. Values reached with exenatide were significantly lower compared to values reached with glimepiride after 12 months ($P<0.05$).</p> <p>Exenatide, but not glimepiride, gave an increase of adiponectin after 12 months ($P<0.05$), and the value registered with exenatide was significantly higher compared to the value recorded with glimepiride at trial end ($P<0.05$).</p> <p>A decrease of tumor necrosis factor-α was observed after 12 months ($P<0.05$) with exenatide, but no with glimepiride; furthermore the value obtained with exenatide was significantly better compared to the value</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				obtained with glimepiride after 12 months ($P<0.05$). Exenatide, but not glimepiride, gave a reduction of high sensitivity CRP after nine and 12 months ($P<0.05$ and $P<0.01$) compared to baseline and glimepiride ($P<0.05$). Secondary: Not reported
Gallwitz et al. ⁷² EUREXA (2012) Exenatide 5 to 10 μ g BID vs glimepiride 1 mg initially, titrated to maximum tolerated dose	MC, OL, RCT Overweight patients aged 18 to 85 years with type 2 diabetes on a stable maximum tolerated dose of metformin with HbA _{1c} between 6.5 and 9.0%	N=977 Average treatment was 2 years	Primary: Time to inadequate glycemic control (HbA _{1c} >9% after the first 3 months, or >7% at 2 consecutive visits 3 months apart after the first 6 months) Secondary: Markers of β -cell function, bodyweight, hypoglycemia, surrogate markers of cardiovascular risk (blood pressure and heart rate)	Primary: Median time to inadequate HbA _{1c} control was 180 weeks with exenatide versus 142.1 weeks with glimepiride ($P=0.032$). In the exenatide group, 203 (41%) patients had treatment failure compared with 262 (54%) in the glimepiride group (risk difference, 12.4; 95% CI, 6.2 to 18.6; HR, 0.748; CI, 0.623 to 0.899; $P=0.002$). Secondary: Systolic blood pressure decreased in patients in the exenatide group (change to endpoint -1.9 mmHg; $P=0.006$), but not in the glimepiride group (1.1 mmHg; $P=0.096$). Heart rate increased at endpoint in patients given exenatide (1.2 beats per min (bpm); $P=0.024$), but not in those given glimepiride (0.6 bpm; $P=0.282$), with no difference between groups at any time. Discontinuation because of adverse events (mainly gastrointestinal) was significantly higher ($P=0.0005$) in the exenatide group than in the glimepiride group in the first six months of treatment, but not thereafter.
Forst et al. ⁷³ (2010) Linagliptin 1, 5, or 10 mg/day vs placebo	AC, DB, MC, PC, PG, RCT Type 2 diabetics 21 to 75 years of age with BMI 25 to 40 kg/m ² , who had inadequate glycemic control on metformin alone	N=333 12 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG and body weight, proportion of patients achieving an	Primary: Placebo corrected decreases in HbA _{1c} were -0.40 ± 0.14 ($P=0.006$), -4.40 ± 0.14 ($P<0.001$), and $-8.00\pm 1.50\%$ ($P<0.001$) with linagliptin 1, 5, and 10 mg, respectively. Treatment with glimepiride significantly decreased HbA _{1c} compared to treatment with placebo -0.68% ($P<0.0001$). Secondary: Decreases in FPG were significantly greater with all doses of linagliptin compared to placebo. The placebo corrected FPG decrease were -1.1 ($P=0.0020$), -1.9 ($P<0.0001$), and -1.6 mmol/L ($P<0.0001$) with linagliptin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>glimepiride (OL) 1 to 3 mg/day</p> <p>Patients were also receiving metformin.</p>	<p>(HbA_{1c} 7.5 to 10.0%)</p>		<p>HbA_{1c} ≤7.0%, proportion of patients with an HbA_{1c} decrease ≥0.5%, safety</p>	<p>1, 5, and 10 mg, respectively.</p> <p>After 12 weeks a small decrease in body weight was observed with all doses of linagliptin (-0.15, -0.57, and -1.27 kg, respectively; P values not reported).</p> <p>Only one (1.4%) patient receiving placebo achieved an HbA_{1c} ≤7.0% compared to ten (approximately 15%), nine (approximately 15%), and 14 (21%) patients receiving linagliptin 1, 5, and 10 mg/day, respectively (P values not reported).</p> <p>A greater proportion of patients receiving linagliptin achieved an HbA_{1c} decrease ≥0.5% compared to patients receiving placebo (43.8 to 53.2 vs 12.9%; P value not reported). In addition, HbA_{1c} decreased by ≥1.0% in 14.1, 27.4, 22.7, and 7.7% with linagliptin 1 mg, linagliptin 5 mg, linagliptin 10 mg, and placebo (P values not reported).</p> <p>Linagliptin was well tolerated. The most commonly reported adverse events were considered to be of mild or moderate intensity; however, ten patients experienced severe adverse events. No episodes of hypoglycemia were reported. Three (4.6%) patients experienced hypoglycemia after dosing with glimepiride.</p>
<p>Yang et al.⁷⁴ (2011)</p> <p>Liraglutide 0.6, 1.2, or 1.8 mg QD</p> <p>vs</p> <p>glimepiride 4 mg QD</p> <p>All patients received metformin.</p>	<p>AC, DB, DD, RCT</p> <p>Adult patients with type 2 diabetes</p>	<p>N=929</p> <p>16 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportions of patients achieving HbA_{1c} <7.0 and ≤6.5%, body weight, BP, hypoglycemia, adverse events</p>	<p>Primary: Baseline HbA_{1c} was significantly reduced with all treatments. Treatment with liraglutide 1.2 and 1.8 mg was non-inferior to glimepiride (mean reduction: 1.36, 1.45, 1.39% points, respectively).</p> <p>Secondary: No significant difference was shown in the proportion of patients achieving HbA_{1c} <7.0 or ≤6.5% between liraglutide 1.2 and 1.8 mg and glimepiride.</p> <p>Liraglutide resulted in a mean reduction in weight of -1.8 to -2.4 kg compared to 0.1 kg weight gain with glimepiride.</p> <p>Liraglutide significantly reduced SBP compared to glimepiride.</p> <p>Two patients receiving glimepiride experienced major hypoglycemia</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>compared to zero patients receiving liraglutide. Liraglutide was associated with a 10-fold lower incidence of minor hypoglycemia compared to glimepiride.</p> <p>Gastrointestinal disorders were the most commonly reported adverse events with liraglutide therapy; events were transient and resulted in few withdrawals.</p>
<p>Charbonnel et al.⁷⁵ (2013)</p> <p>Sitagliptin starting at 100 mg/day, with glimepiride added if further glucose control needed (oral)</p> <p>vs</p> <p>liraglutide starting at 0.6 mg/day, up-titrated to 1.2 mg/day after 1 week (injectable)</p>	<p>AC, OL, RCT</p> <p>Patients with type 2 diabetes mellitus aged 18 to 79 years, on a stable dose of metformin monotherapy $\geq 1,500$ mg/day for ≥ 12 weeks, with an $HbA_{1c} \geq 7.0\%$ and $\leq 11.0\%$ and a fasting fingerstick glucose < 15 mmol/L at the randomization visit, deemed capable by the investigator of using a Victoza pen injection device</p>	<p>N=653 (per protocol patients were analyzed, N=522)</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c} (non-inferiority)</p> <p>Secondary: FPG, plasma lipids, safety</p>	<p>Primary: HbA_{1c} decreased over 26 weeks in both treatment strategy groups, with a larger initial reduction at week 12 in the injectable strategy group. The mean change in HbA_{1c} at week 26 was -1.3% in the oral group and -1.4% in the injectable group. The primary hypothesis was met to declare that the oral treatment was non-inferior to the injectable in lowering HbA_{1c}.</p> <p>Secondary: Significant reductions in FPG at week 26 were observed in both groups, with a greater reduction observed in the injectable group. No meaningful between-group differences were found in any lipid variable or in the incidence of clinical adverse effects overall. The incidence of drug-related adverse events or adverse events leading to discontinuation was greater in the injectable group than in the oral group. These differences were mainly related to the significantly higher incidence of gastrointestinal adverse events, such as abdominal pain, diarrhea, nausea, and vomiting, in the injectable group.</p>
<p>Chogtu et al.⁷⁶ (2009)</p> <p>Glimepiride 2 mg daily and pioglitazone (variable doses)</p> <p>vs</p>	<p>OL, RCT</p> <p>Patients 30 to 70 years of age with type 2 diabetes who received glimepiride and required a TZD due to a lack of glycemic control, normotensive, and</p>	<p>N=63</p> <p>12 weeks</p>	<p>Primary: Blood glucose levels, plasma lipids, BP</p> <p>Secondary: Not reported</p>	<p>Primary: The mean change in the FPG and PPG from baseline to week 12 was significant in both groups ($P < 0.05$). There was no significant difference between the groups with regard to the change in FPG ($P = 0.10$) and PPG ($P = 0.95$).</p> <p>HbA_{1c} levels also decreased from baseline to week 12. There was no significant difference between the treatment groups ($P > 0.05$).</p> <p>At week 12, 37.9% of patients in the pioglitazone group and 17.8% of</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glimepiride 2 mg daily and rosiglitazone (variable doses)	not on antilipemic therapy			<p>patients in the rosiglitazone group had HbA_{1c} <7.0% (P value not reported).</p> <p>TC decreased in both treatment groups; however, to a greater extent with pioglitazone compared to rosiglitazone (P=0.004). TG in the pioglitazone group (P=0.0006) decreased significantly in comparison to the rosiglitazone group (P=0.255) at 12 weeks (P=0.002 pioglitazone vs rosiglitazone). LDL-C decreased significantly (P=0.005) in the pioglitazone group compared to the rosiglitazone group. There was no significant difference in HDL-C among the treatment groups (P>0.05).</p> <p>There was no change in SBP with pioglitazone or rosiglitazone from baseline to week 12. There was also no significant difference in SBP between the treatment groups (P=0.45).</p> <p>There was an increase in the weight following treatment with pioglitazone and rosiglitazone; however, there was no difference between the groups (P=0.10).</p> <p>Secondary: Not reported</p>
<p>Chou et al.⁷⁷ (2008)</p> <p>Glimepiride 1mg titrated to 4 mg QD (GLIM)</p> <p>vs</p> <p>rosiglitazone 4 mg titrated to 8 mg QD (RSG)</p> <p>vs</p> <p>rosiglitazone/ glimepiride</p>	<p>DB, MC, PG, RCT</p> <p>Type 2 diabetics, HbA_{1c} 7.5 to 12.0%, fasting C-peptide ≥0.8 ng/mL, FPG ≥126 mg/dL, who had been treated with diet and/or exercise alone or who had not taken oral antidiabetic medication or insulin for >15 days in the preceding 4 months</p>	<p>N=901</p> <p>28 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, proportion of patients achieving HbA_{1c} and FPG targets, HOMA-S, HOMA-B, cardiovascular biomarkers, safety</p>	<p>Primary: Both rosiglitazone/glimepiride regimens significantly reduced HbA_{1c} to a greater extent than glimepiride or rosiglitazone monotherapy regimens (P<0.0001).</p> <p>Secondary: A significantly greater reduction in FPG levels was observed in the rosiglitazone/glimepiride group compared to the glimepiride or rosiglitazone monotherapy groups (P<0.0001).</p> <p>Significantly more patients achieved HbA_{1c} target levels ≤6.5 and <7.0% with either rosiglitazone/glimepiride regimen than patients with glimepiride or rosiglitazone monotherapy regimens (P<0.0001).</p> <p>Improvement in CRP was also observed in patients treated with rosiglitazone/glimepiride or rosiglitazone monotherapy compared to patients treated with glimepiride monotherapy (P<0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
4/1 mg titrated to 4/4 mg (regimen A) or titrated to 8/4 mg QD (regimen B) (RSG/GLIM)				There were no new safety or tolerability issues identified from its monotherapy components and a similar adverse event profile was observed across the fixed-dose regimens. The most commonly reported adverse event was hypoglycemia and the incidence of confirmed symptomatic hypoglycemia (3.6 to 5.5%) was comparable among subjects treated with a fixed-dose regimen and glimepiride monotherapy.
McCluskey et al. ⁷⁸ (2004) Glimepiride 2 to 8 mg QD and rosiglitazone (existing therapy) vs rosiglitazone (existing therapy)	MC, PC, RCT Patients with type 2 diabetes poorly controlled (HbA _{1c} 7.5 to 9.5%) with rosiglitazone monotherapy	N=40 30 weeks	Primary: Effect on HbA _{1c} Secondary: Effect on FPG, body weight, lipoproteins, proportion of patients who achieved HbA _{1c} and FPG targets	Primary: Significant reductions in HbA _{1c} were observed with glimepiride (-1.2%) compared to placebo (-0.3%; P<0.001). Secondary: Significant reductions in FPG were observed with glimepiride (-24.41 mg/dL) compared to placebo (5.9 mg/dL; P<0.008). Significantly greater proportion of patients receiving glimepiride achieved the target HbA _{1c} ≤7.0% (60.0 vs 14.3%; P<0.008). There were no significant differences between treatment groups in TC, HDL-C, LDL-C, or TG at any time during study period.
Rosenstock et al. ⁷⁹ (2008) <u>Study A</u> Glimepiride 3 mg QD and rosiglitazone 4 mg QD (RSG 4 mg + GLIM) vs glimepiride 3 mg QD and rosiglitazone 8 mg QD (RSG 8 mg + GLIM)	2 DB, PC, RCT Patients 40 to 80 years of age (Study A) or 18 to 75 years of age (Study B) with type 2 diabetes, HbA _{1c} ≥7.0% and FPG 126 to 270 mg/dL at baseline; in the 3 months prior to enrolment, eligible patients in Study A received monotherapy with an oral antidiabetic	N=174 (Study A) N=391 (Study B) 26 weeks (Study A) 24 weeks (Study B)	Primary: Mean change in baseline HbA _{1c} Secondary: Proportion of patients with HbA _{1c} <7.0% and/or HbA _{1c} reduction ≥0.7% at the end of the treatment period, mean change in baseline FPG	<u>Study A</u> Primary: At week 26, the mean change in HbA _{1c} from baseline was -0.63% in the RSG 4 mg+GLIM (P=0.03 vs GLIM 3 mg), -1.17% in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -0.08% in the GLIM 3 mg group. Secondary: The mean change in FPG from baseline was -21 mg/dL in the RSG 4 mg+GLIM (P=0.09 vs GLIM alone), -43 mg/dL in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -2 mg/dL for GLIM 3 mg. At week 26, 43% of patients achieved HbA _{1c} <7.0% in the RSG 4 mg+GLIM group (P=0.0129 vs GLIM alone) and 68% achieved the same HbA _{1c} goal in the RSG 8 mg+GLIM group (P=0.0001 vs GLIM 3 mg) compared to 32% in the GLIM 3 mg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>glimepiride 3 mg QD (GLIM alone)</p> <p><u>Study B</u> Glimepiride 2 to 4 mg QD and rosiglitazone 4 mg QD (RSG add-on)</p> <p>vs</p> <p>glimepiride 4 to 8 mg QD and placebo (GLIM)</p>	<p>agent; eligible patients in Study B were treated with a non-TZD oral antidiabetic therapy for ≥ 3 months prior to screening, including metformin monotherapy, sulfonylurea monotherapy, or low-dose combination therapy with metformin and sulfonylurea</p>			<p><u>Study B</u> Primary: At week 24, the mean change in HbA_{1c} from baseline was -0.68% in the RSG add-on group compared to -0.08% in the GLIM 4 to 8 mg group (P<0.0001).</p> <p>Secondary: The mean change in FPG from baseline was -28 mg/dL in the RSG add-on group compared to -1 mg/dL in the GLIM 4 to 8 mg group (P<0.0001).</p> <p>At week 24, 39% of patients achieved HbA_{1c} <7.0% in the RSG add-on group compared to 15% in the GLIM 4 to 8 mg group (P<0.0001).</p> <p>Insulin sensitivity increased significantly in the RSG add-on group but was unchanged with GLIM 4 to 8 mg. β-cell function increased over 24 weeks in both treatment groups but with a significantly greater increase with RSG add-on group.</p> <p>RSG add-on significantly reduced fasting levels of C-peptide (P=0.025), proinsulin (P=0.0006), and insulin (P=0.013) and reduced the proinsulin:insulin ratio (P<0.0001). There were no significant changes in any of these parameters with GLIM 4 to 8 mg (C-peptide; P=0.075, proinsulin; P=0.42, insulin; P=0.10 and proinsulin:insulin ratio; P=0.34).</p>
<p>Schernthaner et al.⁸⁰ (2015) GENERATION</p> <p>Glimepiride ≤ 6 mg/day</p> <p>vs</p> <p>saxagliptin 5 mg/day</p>	<p>DB, MC, RCT</p> <p>Patients with type 2 diabetes ≥ 65 years of age on stable metformin monotherapy at any dose for ≥ 8 weeks before enrolment and had an HbA_{1c} concentration of 7.0 to 9.0%</p>	<p>N=720</p> <p>52 weeks</p>	<p>Primary: HbA_{1c} <7.0% without confirmed/severe hypoglycaemia</p> <p>Secondary: Incidence of confirmed/severe hypoglycaemia</p>	<p>Primary: The proportions of patients achieving HbA_{1c} <7.0% at week 52 without confirmed/severe hypoglycaemia were similar with saxagliptin and glimepiride: 37.9 vs 38.2% (OR, 0.99; 95% CI, 0.73 to 1.34; P=0.9415); however, a significant treatment-by-age interaction was detected (P=0.0389).</p> <p>Secondary: Fewer patients in the saxagliptin group experienced ≥ 1 confirmed/severe hypoglycaemic event over the treatment period, compared with the glimepiride group: 1.1 vs 15.3% (OR, 0.06; 95% CI, 0.02 to 0.17; nominal P<0.0001).</p>
<p>Schernthaner et al.⁸¹</p>	<p>MC, OL, RCT</p>	<p>N=310</p>	<p>Primary: Changes in HbA_{1c}.</p>	<p>Primary: Significant changes from baseline in HbA_{1c} were observed at 52, 78, 104</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2015) EUREXA</p> <p>TZD or glimepiride added to metformin plus exenatide twice daily</p> <p>vs</p> <p>exenatide twice daily added to metformin plus glimepiride</p>	<p>Patients with type 2 diabetes with metformin failure (HbA_{1c} ≥6.5 to ≤9.0%), were 19 to 85 years of age, and had a BMI of ≥25 to ≤40 kg/m²</p>	<p>Median duration of 2 years</p>	<p>BMI, lipids, hypoglycaemia, and vital signs</p> <p>Secondary: Not reported</p>	<p>and 130 weeks with add-on TZD (all P<0.01), but only at 52 weeks with add-on glimepiride (P=0.001). Significant between-group differences favouring add-on TZD were observed at 78 (P=0.004) and 130 weeks (P=0.001).</p> <p>Among patients re-randomized to add-on glimepiride and add-on TZD, HbA_{1c} ≤7.0% was achieved by 26.0 and 30.7%, respectively, and HbA_{1c} ≤6.5% by 8.2 and 9.3%, respectively (no significant differences between the randomized groups).</p> <p>BMI significantly increased from baseline at 52, 78, 104 and 130 weeks with add-on TZD (all P≤0.01), but significantly increased at 52 and 78 weeks (both P<0.05) and decreased at 130 weeks with add-on glimepiride; the between-group difference was significant at 104 (P=0.022) and 130 weeks (P=0.008).</p> <p>HDL cholesterol significantly increased from baseline to 130 weeks in the TZD add-on group (P<0.001), but not in the add-on glimepiride group; the between-group difference significantly favoured TZD (P<0.001). For total and LDL cholesterol, there were no significant within- or between-group changes from baseline to 130 weeks.</p> <p>Systolic blood pressure was significantly increased at 130 weeks with add-on TZD (P=0.043), but not with add-on glimepiride; the between-group difference significantly favoured glimepiride (P=0.044).</p> <p>The incidence of any hypoglycaemia and nocturnal, non-nocturnal and documented symptomatic hypoglycaemia with blood glucose ≤70 mg/dl was significantly higher for glimepiride than TZD as add-on to exenatide plus metformin. Although the proportion of patients reporting documented symptomatic hypoglycaemia with blood glucose <50 mg/dl was similar in the add-on glimepiride (1/74; 1.4%) or TZD (1/76; 1.3%) groups, the exposure-adjusted mean rate/year was higher in the glimepiride group (0.10 vs 0.01 events/year of patient exposure).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Bao et al.⁸² (2010)</p> <p>Glipizide XL</p> <p>vs</p> <p>glipizide XL plus acarbose</p>	<p>AC, OL, RCT</p> <p>Newly diagnosed type 2 diabetics, 30 to 70 years of age, with HbA_{1c} 7.0 to 9.8%, and no prior use of antidiabetic medications</p>	<p>N=40</p> <p>8 weeks</p>	<p>Primary: Glycemic control, improvements in insulin secretion and sensitivity, glycemic variability, hypoglycemia</p> <p>Secondary: Not reported</p>	<p>Primary: After eight weeks, FPG, two-hour post-oral glucose tolerance test plasma glucose, mean blood glucose, HbA_{1c}, glycated albumin, and HOMA-IR were significantly decreased with both treatments. HOMA-B increased significantly compared to baseline (P<0.01 for both). Compared to glipizide XL, combination therapy had significantly lower mean blood glucose and HOMA-IR values after eight weeks (P<0.05 for both). Mean changes in mean blood glucose, HbA_{1c}, and glycated albumin were all greater with combination therapy compared to monotherapy, with only differences in mean blood glucose reaching significant. The overall glucose-lowering and -stabilizing effects were more pronounced with combination therapy.</p> <p>Over the duration of the trial, the decreases in mean amplitude of glycemic excursions and AUC_{postprandial incremental} were significant with both treatments (P<0.01). There was also a significant decrease in mean of daily differences with combination therapy compared to baseline (P<0.01). Patients receiving combination therapy had significantly lower mean of daily differences, mean amplitude of glycemic outcomes, and AUC_{postprandial incremental} values compared to patients receiving monotherapy after eight weeks (P<0.05 for all).</p> <p>There were no significant between-group differences in either the frequency or the duration of hypoglycemia. The mean duration of hypoglycemia was 88.8±84.7 minute per event with monotherapy and 176.3±123.5 minute per event with combination therapy (P=0.114). Patients receiving monotherapy had 0.7±0.4 events per day compared to 0.8±0.4 events per day in patients receiving combination therapy (P=0.612). There was no difference in total instances of severe hypoglycemia reported.</p> <p>Secondary: Not reported</p>
<p>Rosenstock et al.⁸³ (2013)</p> <p>Alogliptin 25 mg QD</p>	<p>AC, DB, PRO, RCT</p> <p>Patients aged 65 to 90 years of age with type 2 diabetes on diet and exercise</p>	<p>N=441</p> <p>52 weeks</p>	<p>Primary: HbA_{1c} changes at week 52 from baseline.</p> <p>Secondary:</p>	<p>Primary: Glycemic control with alogliptin was comparable to that with glipizide, with no statistically significant treatment-group differences for any of the corresponding efficacy endpoints.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glipizide 5 mg (titrated to 10 mg if needed)	therapy alone during the 2 months prior to screening with HbA _{1c} level of 6.5 to 9.0% or on oral antidiabetic monotherapy with HbA _{1c} of 6.5 to 8.0%		Changes from baseline in HbA _{1c} at all time points, changes in FPG, 2- hour PPG, weight and lipid changes, and adverse events	Treatment with alogliptin resulted in modest body weight decreases throughout the study, which were significant when compared with the increases observed with glipizide, -0.62 vs 0.60 kg, respectively, by week 52 (P<0.001). Triglycerides also significantly improved with alogliptin (8.0% decrease) compared with glipizide (1.2% increase; P=0.046), whereas no significant differences were noted for total cholesterol (0.4 vs 0.3% decrease), high-density lipoprotein cholesterol (1.7 vs 0.6% increase) or low-density lipoprotein cholesterol (0.8% increase vs 1.3% decrease). Fewer patients discontinued from alogliptin because of adverse events (8.6 vs 12.3% from glipizide).
Del Prato et al. ⁸⁴ (2014) Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs glipizide 5 mg QD, titrated to a maximum of 20 mg	DB, MC, RCT Patients 18 to 80 years of age with type 2 diabetes inadequately controlled on stable- dose metformin	N=2,639 104 weeks	Primary: Mean change from baseline in HbA _{1c} Secondary: Changes over time in HbA _{1c} and FPG, incidence of clinical response (HbA _{1c} ≤6.5 and ≤7.0%), changes in body weight, incidence of hyperglycaemic rescue, and changes in 2-h PPG over time	Primary: From baseline HbA _{1c} values of 7.6% in all three treatment groups, changes up to weeks 52 and 104 showed sustained glycaemic response. In the analysis of mean differences between the treatment groups at week 104, the criteria for non-inferiority to glipizide were satisfied for both alogliptin 12.5 mg (P<0.001) and alogliptin 25 mg (P<0.001), and the criteria for superiority to glipizide were satisfied for alogliptin 25 mg (P=0.010). Secondary: FPG concentration decreased by 0.05 and 0.18 mmol/l for alogliptin 12.5 and 25 mg, respectively, and increased by 0.30 mmol/l for glipizide (P<0.001 for both comparisons with glipizide). Mean weight changes were -0.68, -0.89 and 0.95 kg for alogliptin 12.5 and 25 mg and glipizide, respectively (P<0.001 for both comparisons with glipizide). Hypoglycaemia occurred in 23.2% of patients in the glipizide group vs 2.5 and 1.4% of patients in the alogliptin 12.5 and 25 mg groups, respectively.
Del Prato et al. ⁸⁵ (2015) Dapagliflozin vs glipizide	DB, MC, RCT Patients with T2DM, ≥18 years of age, who were previously treated with oral anti- diabetic agents,	N=801 4 year extension study	Primary: Therapeutic glycaemic response defined as HbA _{1c} <7.0% Secondary: FPG, blood	Primary: At 208 weeks, dapagliflozin compared with glipizide produced sustained reductions in HbA _{1c} : -0.30% (95% CI, -0.51 to -0.09), in total body weight: -4.38 kg (95% CI, -5.31 to -3.46) and in systolic blood pressure: -3.67 mmHg (95% CI, -5.92 to -1.41). Secondary: Dapagliflozin was not associated with glomerular function deterioration,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Studied agent added on to OL dosed metformin.	inadequately controlled blood sugar, BMI ≤ 45 kg/m ² and fasting C-peptide ≥ 0.34 ng/mL		pressure, body weight, safety	while this occurred more frequently in patients in the glipizide group. Fewer patients reported hypoglycaemia in the dapagliflozin compared with the glipizide group (5.4 vs 51.5%). Genital and urinary tract infections were more common with dapagliflozin than with glipizide, but their incidence decreased with time and all events responded well to antimicrobial treatment.
Goldstein et al. ⁸⁶ (2003) Glipizide 15 mg BID vs metformin 500 to 2,000 mg daily vs glipizide/ metformin 5/500 mg daily (dose titrated up to 4 tablets per day)	DB, MC, PG, RCT Patients with type 2 diabetes and inadequate glucose control (HbA _{1c} 7.5 to 12.0%) despite monotherapy with at least half the maximum labeled daily dose of a sulfonylurea, FPG <300 mg/dL, and BMI ≥ 25 to ≤ 40 kg/m ²	N=247 18 weeks	Primary: Change in HbA _{1c} Secondary: Changes in FPG, three-hour PPG, area under the concentration-time curve (AUC), three-hour postprandial insulin incremental AUC during three hours after a standard test meal, fasting insulin level, serum lipid profiles, body weight	Primary: The decreases in HbA _{1c} were significantly greater in the glipizide/metformin group compared to either of the monotherapy groups (P<0.001). A total of 36.6% of patients receiving glipizide/metformin, 8.9% of patients receiving glipizide, and 9.9% of patients receiving metformin had an HbA _{1c} <7.0% at the final visit. Secondary: Combination therapy reduced the FPG from baseline significantly more compared to glipizide and metformin monotherapies (P<0.001). Combination therapy controlled PPG more than metformin monotherapy or glipizide monotherapy, as measured using a three-hour incremental AUC (P=0.002, and P<0.001, respectively). The postprandial insulin three-hour incremental AUC increased from baseline with combination therapy, and decreased with glipizide monotherapy; the differences between these groups were not significant. There was a decrease in the postprandial insulin AUC in the metformin monotherapy group, which was significant (P<0.001 vs combination group). Fasting insulin decreased in the combination therapy group and in the metformin monotherapy group. Fasting insulin increased in the glipizide monotherapy group. The changes in the combination therapy group did not differ significantly from either monotherapy group. There were decreases in body weight in all groups, -0.3 kg with the combination therapy group, -0.4 kg with the glipizide monotherapy group, and -2.7 kg in the metformin monotherapy group. The changes in the metformin monotherapy group were significant compared to the combination therapy group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Göke et al.⁸⁷ (2013)</p> <p>Saxagliptin 5 mg/day</p> <p>vs</p> <p>glipizide 5 to 20 mg/day</p> <p>Both treatments as an add-on to metformin</p>	<p>AC, DB, MC, RCT</p> <p>Adults with type 2 diabetes and inadequate glycemic control on metformin alone (HbA_{1c} > 6.5 to 10%)</p>	<p>N=858</p> <p>52 week initial phase followed by 52 week extension phase</p>	<p>Primary: Non-inferiority in mean change from baseline HbA_{1c}, safety and tolerability</p> <p>Secondary: Not reported</p>	<p>There were no significant changes in the fasting lipid profile in the combination group or metformin monotherapy group. There were significant increases from baseline in TC and TG in the glipizide monotherapy group.</p> <p>Primary: Improvement in HbA_{1c} at week 104 was similar with saxagliptin + metformin and glipizide + metformin. At week 104, the adjusted mean ±SE change from baseline HbA_{1c} was -0.41±0.04% with saxagliptin + metformin and -0.35±0.04% with glipizide + metformin [a between-group difference of -0.05% (95% CI, -0.17 to 0.06%)].</p> <p>Over the course of the 104-week study, 896 hypoglycemic events were reported in 165 patients (38.4%) in the glipizide + metformin group, and 24 hypoglycemic events were reported in 15 patients (3.5%) in the saxagliptin + metformin group (difference, -34.9%; 95% CI for difference, -39.8 to -30.0%). Most of these events occurred during the initial 52 weeks.</p> <p>Over the course of the study, mean body weight decreased in the saxagliptin + metformin group and increased in the glipizide + metformin group.</p> <p>Secondary: Not reported</p>
<p>Garber et al.⁸⁸ (2002)</p> <p>Glyburide 2.5 mg daily</p> <p>vs</p> <p>metformin 500 mg daily</p> <p>vs</p> <p>glyburide/metformin</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with type 2 diabetes with inadequate glycemic control with diet and exercise, HbA_{1c} >7.0%, normal renal and liver function, and a BMI ≤38 kg/m²</p>	<p>N=806</p> <p>20 weeks</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: Changes in FPG, two-hour PPG, fasting and two-hour insulin levels, serum lipid concentrations, body weight</p>	<p>Primary: Patients in both glyburide/metformin groups had significantly greater mean reduction from baseline HbA_{1c} (level of 8.2%) compared to the placebo group (P<0.001). The reductions in HbA_{1c} from baseline for each glyburide/metformin group were significantly greater than the placebo or metformin groups (P<0.001). The reduction in HbA_{1c} in the glyburide/metformin 1.25/250 mg group was significantly greater compared to the glyburide group (P<0.016), and for the glyburide/metformin 2.5/500 mg group compared to the glyburide group (P<0.004).</p> <p>Sixty-six percent of the patients in the glyburide/metformin 1.25/250 mg group (P=0.006 vs metformin) and 72% of the patients in the glyburide/metformin 2.5/500 mg group (P<0.001 vs metformin, P=0.037 vs glyburide) had achieved an HbA_{1c} <7.0% compared to 60% of the patients in the glyburide group, 50% of patients in the metformin group, and 20% of</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>1.25/250 mg daily</p> <p>vs</p> <p>glyburide/ metformin 2.5/500 mg daily</p> <p>vs</p> <p>placebo</p> <p>Doses were titrated to a maximum of 4 tablets per day.</p>				<p>patients in the placebo group.</p> <p>Secondary: Mean decreases in FPG concentrations were significantly greater for both combination groups compared to the placebo (P<0.001) and metformin groups (P<0.001). Mean decreases in FPG were numerically greater in both combination groups compared to the glyburide group, but the differences were not significant.</p> <p>Glyburide/metformin 1.25/250 mg group, glyburide/metformin 2.5/500 mg group, and the glyburide group had modest changes in body weight of 1.4, 1.9, and 1.7 kg, respectively, compared to 0.7 and 0.6 kg mean decrease in patients receiving placebo and metformin, respectively. The mean changes in body weight for the glyburide/metformin groups and the glyburide group were significantly different from placebo.</p> <p>There were no significant changes seen in TC, LDL-C, or HDL-C, and TGs with any treatment.</p>
<p>Marre et al.⁸⁹ (2002)</p> <p>Glyburide 5 mg daily</p> <p>vs</p> <p>metformin 500 mg daily</p> <p>vs</p> <p>glyburide/ metformin 2.5/500 mg daily</p> <p>vs</p>	<p>DB, MC, PG, RCT</p> <p>Patients >18 years of age with type 2 diabetes with a FPG \geq126 mg/dL despite treatment with monotherapy metformin \geq850 mg BID or \geq500 mg TID, diet, and exercise for 2 months prior to enrollment, and BMI <40 kg/m²</p>	<p>N=411</p> <p>16 weeks</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: Changes in FPG, fructosamine levels</p>	<p>Primary: Mean HbA_{1c} levels improved in all groups. There were significantly greater reductions in the patients receiving combination therapy as compared to either monotherapy (P<0.05). There were no significant differences in the amount of the reductions in the HbA_{1c} between the two combination therapies or the two monotherapies.</p> <p>Seventy-five percent of the glyburide/metformin 2.5/500 mg group and 63.8% of the glyburide/metformin 5/500 mg group achieved an HbA_{1c} <7.0% as compared to the metformin (37.6%) or glyburide (41.9%) groups (P=0.001 for both).</p> <p>Secondary: FPG decreased in all groups. There were significant improvements in both the combination groups compared to either monotherapy (P<0.05). There were no significant differences in effects on FPG between either of the combination therapies or the monotherapies.</p> <p>Mean decreases in fructosamine in both combination groups were</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glyburide/ metformin 5/500 mg daily Doses were titrated to a maximum of 4 tablets per day.				significantly greater (P<0.05) compared to the changes seen in the monotherapy groups.
DeFronzo et al. ⁹⁰ (1995) <u>Protocol 1:</u> Metformin 850 to 2,550 mg daily vs placebo <u>Protocol 2:</u> Glyburide 5 to 10 mg BID vs metformin 500 to 2,500 mg daily vs glyburide plus metformin	2 DB, PG, RCT Moderately obese patients with type 2 diabetes inadequately controlled by diet (Protocol 1) or diet plus glyburide (Protocol 2)	<u>Protocol 1</u> N=289 29 weeks <u>Protocol 2</u> N=632 29 weeks	Primary: Changes in plasma glucose, HbA _{1c} , plasma insulin, lipids, plasma lactate Secondary: Not reported	Primary: <u>Protocol 1:</u> As compared to the placebo group, the metformin group had lower mean FPG concentrations (189±5 vs 244±6 mg/dL; P<0.001). HbA _{1c} levels were also lower in the metformin group (7.1±0.1 vs 8.6±0.2%; P<0.001). The changes from baseline for TC and LDL-C for metformin were significant compared to placebo (P=0.001 and P=0.019, respectively). Fasting plasma lactate levels were similar at all times during the active-treatment in both groups. <u>Protocol 2:</u> Patients in the metformin plus glyburide combination group, compared to the glyburide alone group, had lower mean FPG concentrations (187±4 vs 261±4 mg/dL; P<0.001), and HbA _{1c} values (7.1±0.1 vs 8.7±0.1%; P<0.001). The effect of metformin alone was similar to that of glyburide alone. The changes from baseline were significant compared to glyburide for the following: TC, metformin (P=0.011) and metformin plus glyburide (P=0.001); LDL-C, metformin (P=0.009) and metformin plus glyburide (P=0.001); and TG, each glyburide and metformin plus glyburide (P=0.001) Fasting plasma lactate did not change in any of the groups in the course of treatment. Secondary: Not reported
Chien et al. ⁹¹ (2007)	DB, MC, PG, RCT	N=100	Primary: Change in baseline	Primary: After 16 weeks, the HbA _{1c} increased in patients receiving glyburide (0.52%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Glyburide 5 mg BID</p> <p>vs</p> <p>metformin 500 mg BID</p> <p>vs</p> <p>glyburide/ metformin 2.5/500mg BID</p> <p>vs</p> <p>glyburide/ metformin 5/500 mg BID</p> <p>Doses were titrated to a maximum of 4 tablets per day.</p>	<p>Patients 30 to 75 years of age with type 2 diabetes, BMI 18.5 to 35.0 kg/m², FPG 140 to 250 mg/dL, and HbA_{1c} 7.0 to 12.0% at the screening visit and FPG ≥140 mg/dL at the second visit, maintained stable sulfonylurea regimen, with or without metformin use</p>	<p>16 weeks</p>	<p>HbA_{1c}</p> <p>Secondary: Change in baseline FPG, adverse events</p>	<p>P=0.0018) and there was no change in patients receiving metformin (0.09%; P value not significant).</p> <p>After 16 weeks, treatment with glyburide/metformin 2.5/500 mg resulted in a greater reduction in HbA_{1c} compared to glyburide or metformin (-1.77%; P<0.001 and -1.34%; P=0.002). Treatment with glyburide/metformin 5/500 mg resulted in a greater reduction in HbA_{1c} compared to glyburide or metformin alone (-1.73%; P<0.001 and -1.30%; P=0.005).</p> <p>After 16 weeks, 19 and 24% of patients in the glyburide/metformin groups (2.5/500 mg and 5/500 mg, respectively) had an HbA_{1c} <7.0% compared to 12.0% in the metformin monotherapy group and 6% in the glyburide monotherapy group.</p> <p>Secondary: Mean changes in FPG from baseline were -43 mg/dL in the glyburide group, -41 mg/dL in the metformin group, -98 mg/dL in the glyburide/metformin 2.5/500mg group, and -101 mg/dL in the glyburide/metformin 5/500 mg group. The two glyburide/metformin groups had significant reductions from baseline compared to the monotherapy groups (P<0.0125 compared to glyburide and metformin).</p> <p>Treatment with glyburide/metformin 2.5/500 mg resulted in a 55 mg/dL reduction in FPG compared to glyburide (P=0.001) and a 57 mg/dL reduction in FPG compared to metformin (P=0.001). Treatment with glyburide/metformin 5/500 mg resulted in a in a 58 mg/dL reduction in FPG compared to glyburide (P<0.001) and a 60 mg/dL reduction in FPG compared to metformin (P=0.001).</p> <p>Ninety-eight episodes of adverse events were reported from the screening visit to the end of the study. Four (14.3%) patients reported adverse events associated with hypoglycemia in the glyburide/metformin 2.5/500 mg group, and two (8.3%) patients reported adverse events associated with gastrointestinal disease among all patients who took metformin during the entire course of the study. The highest incidence of gastrointestinal adverse effects was 32.0% in metformin group, and the lowest was 7.7% in the glyburide/metformin 2.5/500 mg group (P=0.021).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Lewin et al.⁹² (2007)</p> <p>Glyburide 15 mg QD and metformin XR (Glumetza[®]) 1,500 mg QD, 2,000 mg QD, or 1,000 mg BID</p> <p>vs</p> <p>glyburide 15 mg QD</p>	<p>DB, MC, RCT</p> <p>Type 2 diabetic patients 18 to 79 years of age, drug naïve or previously treated with oral antidiabetic medications (monotherapy with any oral antidiabetic medications up to half the maximum therapeutic dose), HbA_{1c} 7.5 to 12.0% in drug-naïve patients or 6.5 to 12.0% in prior drug treatment patients, FPG 200 to 400 mg/dL (drug naïve patients) or 120 to 250 mg/dL (prior drug treatment patients) and C-peptide levels >0.8 ng/mL</p>	<p>N=607</p> <p>30 weeks</p>	<p>Primary: Change baseline HbA_{1c}</p> <p>Secondary: Changes in HbA_{1c} and FPG at week eight, fructosamine, TC, HDL-C, LDL-C, TG, weight, BMI, discontinuation rates, adverse events</p>	<p>Primary: There were significant reductions in HbA_{1c} from baseline to week 30 in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (-0.74 vs 0.08%, respectively; P<0.001).</p> <p>Secondary: There were significant reductions from baseline in mean FPG and in mean HbA_{1c} at week eight in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (P<0.001).</p> <p>There were significant differences between the combined metformin and sulfonylurea groups and the monotherapy group for mean changes in fructosamine, TC, HDL-C, and LDL-C (P<0.001 for all).</p> <p>There were significant increases from baseline in mean weight and BMI in the monotherapy sulfonylurea group (P<0.001). In comparison, there was no significant change in weight and a smaller increase in mean BMI in the combined metformin and sulfonylurea groups (P=0.028).</p> <p>There was a significant difference in the rates of hypoglycemia between groups, which were 11.6% in the combined metformin and sulfonylurea groups and 4.2% in the monotherapy sulfonylurea group (P=0.007). However, no significant difference between these two groups was observed for gastrointestinal events.</p> <p>Forty patients (9.3%) in the combined metformin and sulfonylurea groups and three patients (2.1%) in the monotherapy sulfonylurea group discontinued treatment due to an adverse event, mainly hypoglycemia (P=0.001).</p>
<p>Nauck et al.⁹³ (2009) LEAD-2</p> <p>Liraglutide 0.6, 1.2, and 1.8 mg SC QD</p>	<p>AC, DB, DD, MC, PG, RCT</p> <p>Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral</p>	<p>N=1,091</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Changes in baseline body weight, FPG,</p>	<p>Primary: HbA_{1c} decreased by -0.7±0.1% with liraglutide 0.6 mg, -1.0±0.1% with liraglutide 1.2 and 1.8 mg, and increased by 0.1±0.1% with glimepiride and placebo. Based on the estimated treatment differences, liraglutide had more efficacious glycemic control compared to placebo (liraglutide 0.6 mg vs placebo, -0.8%; 95% CI, -1.0 to -0.6 and liraglutide 1.2 and 1.8 mg vs placebo, -1.1%; 95% CI, -1.3 to -0.9; P values not reported). Analysis of the estimated treatment difference in HbA_{1c} between liraglutide and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs placebo</p> <p>vs glimepiride 4 mg/day</p> <p>All patients also received metformin 1,500 to 2,000 mg/day.</p>	<p>glucose lowering agent monotherapy ≥ 3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy ≥ 3 months), and BMI ≤ 40 kg/m²</p>		<p>seven-point self-monitored glucose concentrations, and β cell function</p>	<p>glimepiride demonstrated that liraglutide 1.2 and 1.8 mg were noninferior to treatment with glimepiride.</p> <p>Secondary: Weight loss was dose-dependent with liraglutide (liraglutide 0.6 mg, -1.8\pm0.2 kg; liraglutide 1.2 mg, -2.6\pm0.2 kg; liraglutide 1.8 mg, -2.8\pm0.2 kg). Reductions in weight with liraglutide were significantly different compared to glimepiride (-1.0\pm0.2 kg; P<0.001). Weight loss with liraglutide 1.2 and 1.8 mg was significantly greater compared to placebo (1.5\pm0.3 kg; P\leq0.01).</p> <p>Decreases in FPG with liraglutide (-1.1, -1.6, and -1.7 mmol/L with liraglutide 0.6, 1.2, and 1.8 mg) were significantly greater compared to the increase with placebo (0.4 mmol/L; P<0.0001). Decreases with liraglutide were similar to glimepiride (-1.3 mmol/L; P value not reported).</p> <p>Mean baseline PPG values decreased with all liraglutide doses and glimepiride (liraglutide 0.6 mg, -1.7 mmol/L; liraglutide 1.2 mg, -2.3 mmol/L; liraglutide 1.8 mg, -2.6 mmol/L; glimepiride, -2.5 mmol/L; placebo, -0.6 mmol/L; P<0.001 for comparisons of all liraglutide doses vs placebo). The decreases observed with liraglutide 1.2 and 1.8 mg were comparable to glimepiride (P values not reported).</p> <p>No differences in the fasting C-peptide values were observed between liraglutide and glimepiride or placebo (P values not reported).</p> <p>Decreases in the proinsulin: insulin ratio with all three liraglutide doses (-0.1) were comparable to glimepiride (P value not reported), and were significantly greater compared to placebo (0.1; P<0.0001).</p> <p>Liraglutide 0.6, 1.2, and 1.8 mg had improvements in HOMA-B of 63, 70, and 71%. Glimepiride had similar improvements, and there were no improvements with placebo. No differences were observed between any of the treatments (P values not reported).</p>
<p>Marre et al.⁹⁴ (2009) LEAD-1</p>	<p>AC, DB, DD, MC, PG, RCT</p> <p>Type 2 diabetic</p>	<p>N=1,041</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p>	<p>Primary: After 26 weeks, HbA_{1c} decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo</p> <p>vs</p> <p>placebo plus glimepiride 2 to 4 mg/day</p> <p>vs</p> <p>placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day</p>	<p>patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥ 3 months, HbA_{1c} 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤ 45 kg/m²</p>		<p>Secondary: Proportion of patients reaching HbA_{1c} (<7.0 and $\leq 6.5\%$), FPG (5.0 to ≤ 7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP</p>	<p>mg, -1.4% (95% CI, 1.6 to -1.1; P<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; P<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; P<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; P<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were more efficacious compared to treatment with rosiglitazone (P<0.0001 for both measures). Decreases in HbA_{1c} were greater in patients previously on an oral glucose lowering agent monotherapy.</p> <p>Secondary: The proportion of patients reaching HbA_{1c} targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached HbA_{1c} <7.0 and $\leq 6.5\%$ compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching HbA_{1c} targets were greater compared to patients receiving placebo (P<0.0001) and rosiglitazone (P<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (P=0.018).</p> <p>The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; P=0.002), 1.2 mg (37%; P<0.001), and 1.8 mg (38%; P=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively).</p> <p>The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported).</p> <p>Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported).</p> <p>Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P\leq0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>rosiglitazone ($P < 0.05$), and increases were only significant compared to placebo with liraglutide 1.2 mg ($P = 0.01$). No differences between treatments were observed for changes in HOMA-IR.</p> <p>Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported).</p>
<p>Chacra et al.⁹⁵ (2010)</p> <p>Glyburide 7.5 to 15 mg daily and saxagliptin 2.5 mg QD</p> <p>vs</p> <p>glyburide 7.5 to 15 mg daily and saxagliptin 5 mg QD</p> <p>vs</p> <p>glyburide 2.5 to 15 mg daily and placebo</p>	<p>DB, MC, RCT</p> <p>Type 2 diabetics 18 to 77 years of age with inadequate glycemic control ($HbA_{1c} \geq 7.5$ to $\leq 10.0\%$), on a submaximal sulfonylurea dose for ≥ 2 months before screening, fasting C-peptide ≥ 1 ng/mL, and BMI ≤ 40 kg/m²</p>	<p>N=768</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and PPG AUC_{0-3hr}, proportion of patients achieving an $HbA_{1c} < 7.0\%$, safety</p>	<p>Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (-0.54 and -0.64 vs 0.08%; $P < 0.0001$ for both).</p> <p>Secondary: Saxagliptin significantly decreased FPG compared to placebo (2.5 mg; $P = 0.0218$ and 5 mg; $P = 0.002$).</p> <p>Saxagliptin significantly decreased PPG AUC_{0-3hr} compared to placebo (-4,296 and -5,000 vs 1,196 (mg/minute)/(dL); $P < 0.0001$ for both).</p> <p>A significantly greater proportion of patients receiving saxagliptin achieved an $HbA_{1c} < 7.0\%$ compared to patients receiving placebo (22.4 and 22.8 vs 9.1%; $P < 0.0001$ for both).</p> <p>Overall saxagliptin was well tolerated. The proportion of patients reporting any adverse event was similar across all treatments; with no evidence of a dose-response relationship. The proportion of patients reporting at least one adverse event and at least one treatment-related adverse event was 75.0 and 19.8, 72.3 and 21.3, and 76.8 and 14.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. No events of Stevens-Johnson syndrome or angioedema were reported. Cardiac disorder events were: 2.0, 4.0 and 3.7% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. Hypertension was reported in 3.6, 6.3, and 2.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo; however, mean SBP and DBP decreased with all treatments. There was no difference in the incidence of reported and confirmed hypoglycemic events with saxagliptin compared to placebo ($P > 0.05$). Confirmed hypoglycemia occurred in 2.4, 0.8, and 0.7% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo.</p>
<p>Goke et al.⁹⁶</p>	<p>DB, NI, RCT</p>	<p>N=858</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2010)</p> <p>Saxagliptin 5 mg/day</p> <p>vs</p> <p>glipizide 5 mg/day, titrated up to 20 mg/day</p>	<p>Patients ≥ 18 years of age with type 2 diabetes with type 2 diabetes, HbA_{1c} > 6.5 to 10.0%, and inadequate glycemic control on metformin alone</p>	<p>52 weeks</p>	<p>Change in baseline HbA_{1c}</p> <p>Secondary: Hypoglycemia, safety</p>	<p>The per protocol analysis demonstrated non-inferiority of saxagliptin vs glipizide; adulated mean changes from baseline HbA_{1c} were -0.74 vs -0.80%, respectively; the between-group difference was 0.06% (95% CI, -0.05 to 0.16).</p> <p>There was a significantly smaller risk in HbA_{1c} (%/week) from week 24 to 52 with saxagliptin vs glipizide (0.001 vs 0.004%; $P=0.04$) indicating a sustained glycemic effect beyond week 24.</p> <p>Secondary: Treatment with saxagliptin vs glipizide was associated with a significantly smaller proportion of patients with hypoglycemic events (3.0 vs 36.3%; $P<0.0001$) and a divergent impact on body weight (adjusted mean change from baseline, -1.1 vs 1.1 kg; $P<0.0001$).</p> <p>Excluding hypoglycemic events, the proportion of patients reporting adverse events was smaller with glipizide (60.0 vs 56.7%); however, treatment-related adverse events were less common with saxagliptin (9.8 vs 31.2%), attributable to the higher frequency of hypoglycemia with glipizide. Discontinuation rates resulting from adverse events were similar (approximately 4%).</p>
<p>Arechavaleta et al.⁹⁷ (2011)</p> <p>Sitagliptin 100 mg/day</p> <p>vs</p> <p>glimepiride 1 mg/day, titrated up to 6 mg/day</p>	<p>DB, NI, RCT</p> <p>Patients with type 2 diabetes, HbA_{1c} 6.5 to 9.0%, and on a stable dose of metformin ($\geq 1,500$ mg/day) combined with diet and exercise for ≥ 12 weeks</p>	<p>N=1,035</p> <p>30 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary Proportions of patients achieving HbA_{1c} $< 7.0\%$, change in baseline FPG, hypoglycemia, body weight</p>	<p>Primary: After 30 weeks, the least squares mean change in HbA_{1c} from baseline was -0.47% with sitagliptin compared to -0.54% with glimepiride, with a between-group difference of 0.07% (95% CI, -0.03 to 0.16). This result met the prespecified criterion for declaring non-inferiority.</p> <p>Secondary: The proportions of patients with HbA_{1c} $< 7.0\%$ at week 30 were 52 and 60% with sitagliptin and glimepiride, respectively.</p> <p>The least squares mean change in FPG from baseline was -0.8 mmol/L (95% CI, -1.0 to -0.6) with sitagliptin compared to -1.0 mmol/L (95% CI, -1.2 to -0.8) with glimepiride, for a between-group difference of 0.2 mmol/L (95% CI, -0.1 to 0.4).</p> <p>The proportions of patients who reported hypoglycemia were 7 and 22%</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with sitagliptin and glimepiride (percentage-point difference, -15; $P<0.001$). Relative to baseline, sitagliptin was associated with a mean weight loss compared to a mean weight gain with glimepiride (-0.8 vs 1.2 kg), yielding a between-group difference of -2.0 kg ($P<0.001$).
Srivastava et al. ⁹⁸ (2012) Sitagliptin 50 mg/day, titrated up to 100 mg/day vs glimepiride 1 mg/day, titrated up to 2 mg/day	PG, RCT Patients with type 2 diabetes inadequately controlled with metformin alone	N=50 18 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG and two-hour PPG, body weight, hypoglycemia	Primary: At 18 weeks, both treatments significantly ($P<0.001$) reduced baseline HbA _{1c} (-0.636 vs -1.172%), with 12% of patients receiving sitagliptin and 36% of patients receiving glimepiride achieving target HbA _{1c} . Secondary: Reductions were significant ($P<0.001$) for both treatments in FPG (-15.49 vs -26.84 mg, respectively) and two-hour PPG (-34.28 vs -44.83 mg, respectively). Sitagliptin showed a net decrease in body weight by 0.102 kg, whereas glimepiride showed net increase in body weight by 0.493 kg. Incidence of hypoglycemia was 4 and 8% with sitagliptin and glimepiride.
Seck et al. ⁹⁹ (2011) Sitagliptin vs glimepiride	DB, RCT Patients with type 2 diabetes receiving metformin	N=803 1 year	Primary: Composite endpoint of HbA _{1c} reduction, lack of hypoglycemia, and no body weight Secondary: Not reported	Primary: Both treatments provided similar degrees of glycemic efficacy (least squares mean difference, -0.67%; between-group difference, -0.01; 95% CI, -0.09 to 0.08); however, significantly more patients receiving sitagliptin achieved an HbA _{1c} reduction >0.5% without hypoglycemia and without an increase in body weight (least squares mean difference, -1.5 vs 1.1 kg; $P<0.001$; between-group difference, -2.5 kg; 95% CI, -3.1 to -2.0). Patients receiving glimepiride reported more than 10 times as many events of hypoglycemia compared to patients receiving sitagliptin. Secondary: Not reported
Hermansen et al. ¹⁰⁰ (2007) Sitagliptin 100 mg QD, glimepiride 4	DB, DD, MC, PC, PG, RCT Type 2 diabetics 18 to 75 years of age,	N=441 24 weeks	Primary: Change in baseline HbA _{1c} Secondary:	Primary: Sitagliptin significantly decreased HbA _{1c} ($P<0.001$) compared to placebo (treatment difference, -0.74%; 95% CI, -0.90 to -0.57). Patients who were receiving triple therapy (-0.89%; 95% CI, -1.10 to -0.68) had a significantly greater decrease in HbA _{1c} compared to patients receiving combination

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>to 8 mg daily, and metformin 1,500 to 3,000 mg daily</p> <p>vs</p> <p>sitagliptin 100 mg QD plus glimepiride 4 to 8 mg daily</p> <p>vs</p> <p>glimepiride 4 to 8 mg daily, metformin 1,500 to 3,000 mg daily, and placebo</p> <p>vs</p> <p>glimepiride 4 to 8 mg daily plus placebo</p>	<p>HbA_{1c} 6.7 to 10.6%, and inadequately controlled on glimepiride with or without metformin</p>		<p>Change in baseline FPG, plasma lipids, β cell function, and insulin resistance; safety and tolerability</p>	<p>therapy (-0.57%; 95% CI, -0.82 to -0.32).</p> <p>A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (17.1 vs 4.8%; P<0.001). A significantly greater proportion of patients receiving triple therapy achieved an HbA_{1c} <7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; P<0.001). No difference was observed between combination therapy with glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; P<0.638).</p> <p>Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; P<0.001).</p> <p>Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported).</p> <p>A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; P<0.001). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and QUICKI between the treatments.</p> <p>Sitagliptin significantly increased fasting insulin compared to placebo (1.8 vs 0.1 μIU/mL; P<0.001).</p> <p>Sitagliptin was well tolerated, both in combination with glimepiride and in triple therapy. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed with sitagliptin compared to placebo, with the majority of that difference due to rates of minor to moderate hypoglycemia.</p> <p>A significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted with sitagliptin compared to a slight decrease in weight with placebo (-0.4 kg; 95% CI, -0.8 to 0.1).</p>
<p>Nauck et al.¹⁰¹ (2007)</p>	<p>AC, DB, MC, NI, PG, RCT</p>	<p>N=1,172</p>	<p>Primary: Change in baseline</p>	<p>Primary: In both treatments, the least squares mean HbA_{1c} change from baseline was -</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Sitagliptin 100 mg QD</p> <p>vs</p> <p>glipizide 5 to 20 mg QD</p> <p>All patients received metformin $\geq 1,500$ mg daily.</p>	<p>Patients 18 to 78 years of age with type 2 diabetes who were inadequately controlled ($HbA_{1c} \geq 6.5$ and $\leq 10\%$) on metformin monotherapy</p>	<p>52 weeks</p>	<p>HbA_{1c}</p> <p>Secondary: FPG, fasting insulin, proinsulin, and lipid parameters, β-cell function, insulin resistance and sensitivity, safety and tolerability, change in body weight</p>	<p>0.67% (95% CI, -0.75 to -0.59).</p> <p>A similar proportion of patients reached an HbA_{1c} level $<7.0\%$ in each group (63 vs 59%; difference, 3.9%; 95% CI, -2.8 to 10.7).</p> <p>Secondary: The change in FPG was not significantly different between the two treatments. The least squares change from baseline for sitagliptin was -0.56 mmol/L (95% CI, -0.81 to -0.30) and -0.42 mmol/L for glipizide (95% CI, -0.67 to -0.17). Sitagliptin led to a decrease in fasting proinsulin compared with an increase with glipizide.</p> <p>Patients receiving glipizide demonstrated a higher rate of hypoglycemia as compared to patients receiving sitagliptin (32 vs 5%; $P < 0.001$). No meaningful differences in overall serious clinical adverse events were observed between the two treatments.</p> <p>Body weight significantly decreased with sitagliptin; the least squares mean change from baseline was -1.5 kg (95% CI, -2 to -0.9). Body weight significantly increased with glipizide with a least squares mean change from baseline of 1.1 kg (95% CI, 0.5 to 1.6). The between-treatment difference was -2.5 kg (95% CI, -3.1 to -2.0; $P < 0.001$).</p>
<p>Schwarz et al.¹⁰² (2008)</p> <p>Glyburide 10 mg QD and metformin 2,000 mg QD</p> <p>vs</p> <p>metformin 2,000 mg QD and nateglinide 120 mg TID before meals</p>	<p>AC, DB, MC, RCT</p> <p>Men and women ≥ 65 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤ 15 mmol/L, BMI 22 to 45 kg/m²</p>	<p>N=69</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Change from baseline to week 104 in FPG, two-hour PPG using the incremental area under the curve (AUC_{0-120 min}) of glucose during oral glucose tolerance tests, the</p>	<p>Primary: Similar reductions in HbA_{1c} were seen with both treatments. The average change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group ($-1.2 \pm 0.2\%$) was similar ($P = 0.310$) to that in the glyburide plus metformin group ($-1.2 \pm 0.1\%$). The changes in HbA_{1c} were significant for both groups as compared to baseline ($P < 0.001$) after two years of treatment and there was no significant difference between the groups.</p> <p>Secondary: Mean change in FPG was -26 ± 6 mg/dl in patients receiving nateglinide plus metformin ($P < 0.001$ vs baseline) and -36 ± 6 mg/dL in patients receiving glyburide plus metformin ($P < 0.001$ vs baseline) ($P = 0.234$ between the groups).</p> <p>A non-significant reduction in two-hour PPG from baseline was reported in</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>proportion of patients achieving a target HbA_{1c} <7.0 or ≤6.5%, adverse events</p>	<p>both nateglinide plus metformin and glyburide plus metformin groups (−15±7 mg/dL; P=0.071 and −8±8 mg/dL; P=0.385, respectively).</p> <p>The proportion of patients who achieved a target HbA_{1c} <7.0% in the nateglinide plus metformin group was not significantly different compared to the glyburide plus metformin group (70 vs 65%, respectively; P=0.736).</p> <p>Similar proportions of patients in the nateglinide plus metformin group and the glyburide plus metformin group maintained a target HbA_{1c} ≤6.5% (40 and 60%, respectively; P=0.206).</p> <p>Approximately 94% of patients in the nateglinide plus metformin group and 88% of patients in the glyburide plus metformin group reported one or more adverse events. One mild hypoglycemic event occurred with nateglinide plus metformin treatment vs 8 mild-to-severe hypoglycemic events with glyburide plus metformin treatment (P<0.023).</p>
<p>Derosa et al.¹⁰³ (2009)</p> <p>Glyburide 7.5 to 12.5 mg daily and metformin 1,500 to 3,000 mg daily</p> <p>vs</p> <p>nateglinide 60 mg TID and metformin 1,500 to 3,000 mg daily</p>	<p>MC, DB, PG, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes mellitus, HbA_{1c} >7.0%), BMI 25 to 28 kg/m², and hypertensive (SBP/DBP, >130/≥85 mm Hg)</p>	<p>N=248</p> <p>12 months</p>	<p>Primary: Changes in BMI, FPG and PPG, HbA_{1c}, fasting and postprandial plasma insulin, HOMA index, and lipid profile (TC, LDL-C, HDL-C, TG, apolipoprotein A-I, and apolipoprotein B), SBP, and DBP</p> <p>Secondary: Not reported</p>	<p>Primary: BMI did not show any significant change during the study.</p> <p>A significant reduction in HbA_{1c} was shown after nine months (P<0.05) and 12 months (P<0.01) in the nateglinide group compared to the baseline value. A significant reduction in HbA_{1c} was seen with glyburide after 12 months (P<0.05) compared to baseline. The HbA_{1c} at 12 months was 6.4% in the nateglinide group compared to 7.3% in the glyburide group (P<0.05).</p> <p>After nine and 12 months, mean FPG levels were significantly decreased in the nateglinide and glyburide groups (P<0.05 and P<0.01, respectively) compared to baseline.</p> <p>Significant changes in PPG were found at nine months (P<0.05) in the nateglinide group and after 12 months in glyburide and nateglinide groups (P<0.05 and P<0.01, respectively) compared to baseline.</p> <p>Fasting plasma insulin and PPI did not show any significant change after three, six, nine and 12 months in both groups compared to the baseline.</p> <p>HOMA index decrease was obtained only at 12 months (P<0.05) compared</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>to the baseline value in both groups,</p> <p>No significant change was observed in TC, LDL-C, HDL-C, TG, apolipoprotein A-I, apolipoprotein B, SBP, DBP and heart rate in either group after three, six, nine and 12 months.</p> <p>Secondary: Not reported</p>
<p>Gerich et al.¹⁰⁴ (2003)</p> <p>Nateglinide 120 mg TID before meals and metformin 500 to 2,000 mg daily</p> <p>vs</p> <p>glyburide 1.25 to 10 mg daily and metformin 500 to 2,000 mg daily</p>	<p>DB, MC, RCT (PRESERVE-β Study)</p> <p>Men and women 18 to 77 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG \leq15 mmol/L, BMI 22 to 45 kg/m² and inadequately controlled on diet and exercise</p>	<p>N=428</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline (average of weeks -2 and 0) to week 104</p> <p>Secondary: Change from baseline to week 104 in FPG, and body weight</p>	<p>Primary: Both treatments maintained similar reductions in HbA_{1c}. The mean change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (-1.2\pm0.1%) was similar (P=0.1730) to that in the glyburide plus metformin group (-1.5\pm0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.0001) after one and two years of treatment and there was no significant difference between the groups.</p> <p>Secondary: Mean change in FPG was -1.6\pm0.2 mmol/L in patients in the nateglinide plus metformin group (P<0.0001 vs baseline) and -2.4\pm0.2 mmol/L in patients in the glyburide plus metformin group (P<0.0001 vs baseline; P=0.0078 vs nateglinide plus metformin).</p> <p>Body weight decreased in the nateglinide plus metformin group (-0.4\pm0.4 kg) and increased in the glyburide plus metformin group (0.8\pm0.5 kg). The change from baseline was significant for the glyburide plus metformin group (P=0.0011) only (P=0.8413 for the nateglinide plus metformin group). The difference between groups was statistically significant (P=0.0115).</p>
<p>Wolffenbittel et al.¹⁰⁵ (1999)</p> <p>Repaglinide 0.5 to 4 mg TID before each meal</p> <p>vs</p>	<p>DB, MC, PG, RCT</p> <p>Patients 40 to 75 years of age with type 2 diabetes who were being treated with oral blood glucose-lowering agents and/or diet, BMI 21 to 35</p>	<p>N=424</p> <p>12 months</p>	<p>Primary: Change in HbA_{1c} and FPG from baseline to the final visit</p> <p>Secondary: Change in fasting insulin and lipid levels and four-</p>	<p>Primary: Change in HbA_{1c} levels was not different between groups when compared to baseline. HbA_{1c} levels increased by 0.58% (95% CI, 0.41 to 0.76) in the repaglinide group and by 0.45% (95% CI, 0.22 to 0.69) in the glyburide group.</p> <p>In a subset of patients who were treated previously with diet only, HbA_{1c} decreased significantly more during glyburide treatment (-2.4%) vs repaglinide (-1%; P<0.05). The changes in HbA_{1c} in patients who were already being treated with oral agents were similar, 0.6% in the repaglinide</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glyburide 1.75 to 10.5 mg daily	kg/m ² , and an HbA _{1c} >6.5% when treated with diet only and <12.0% when treated with diet plus oral blood glucose-lowering agents		point blood glucose levels (fasting, before lunch, before supper, and at bedtime) from baseline to the final visit	<p>group and 0.7% in the glyburide group.</p> <p>Changes in fasting plasma glucose from baseline showed a similar trend as the HbA_{1c}.</p> <p>Secondary: Mean fasting insulin levels decreased in the repaglinide group (-3 pmol/L) and increased in the glyburide group (+1 pmol/L). There was no treatment difference.</p> <p>Changes from baseline in four-point glucose levels were small for both treatment groups.</p> <p>Lipid levels (TC, HDL, and TG) did not change during the study.</p>
<p>Cesur et al.¹⁰⁶ (2007)</p> <p>Repaglinide up to 4 mg QD</p> <p>vs</p> <p>glimepiride up to 8 mg QD</p> <p>vs</p> <p>insulin glargine up to 36 U QD</p>	<p>MC, OL, OS, PRO</p> <p>Patient 33 to 67 years of age with type 2 diabetes, HbA_{1c} 6.0 to 8.0% taking oral diabetes agents, who were willing to fast throughout Ramadan month</p>	<p>N=65</p> <p>Duration not specified</p>	<p>Primary: FBG, PPG, HbA_{1c}, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and post-Ramandan fasting</p> <p>Secondary: Not reported</p>	<p>Primary: In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan.</p> <p>In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan (P<0.05 and P<0.01, respectively). At post-Ramadan and one-month post-Ramadan, changes in PPG values in the fasting group were lower compared to the nonfasting group (P<0.01 for both time periods).</p> <p>There was no significant change in HbA_{1c} levels between the nonfasting and fasting groups.</p> <p>There was a significant increase in fructosamine levels in both fasting group and non-fasting group at one-month post-Ramadan (P<0.01 for both).</p> <p>BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group (P<0.05 between pre-Ramadan and post-Ramadan in nonfasting group).</p> <p>TC, LDL and TG did not change throughout the study period but HDL levels significantly increased at post-Ramadan in the fasting group (P<0.01).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>In nonfasting group, LDL and TG levels significantly increased at post-Ramadan (P<0.05 for both).</p> <p>At least one hypoglycemia episode was reported in 12.2% of patients in the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10.0% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia.</p> <p>Secondary: Not reported</p>
<p>Standl et al.¹⁰⁷ (2001)</p> <p>Glyburide 3.5 to 5 mg BID to QID, metformin 500 to 850 mg daily, and miglitol 25 mg to 100 mg TID</p> <p>vs</p> <p>glyburide 3.5 to 5 mg BID to QID, metformin 500 to 850 mg daily, and placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 30 to 70 years of age with type 2 diabetes for at least 3 years, HbA_{1c} ≥7.5 to ≤10.5%, BMI ≤35 kg/m², stable body weight over the previous 3 months, and inadequately controlled on combination therapy of diet, glibenclamide* and metformin</p>	<p>N=154</p> <p>24 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: FPG, PPG, fasting and postprandial serum insulin and TG levels, and urinary glucose</p>	<p>Primary: Addition of miglitol to sulfonylureas and metformin produced a significant reduction in HbA_{1c} (−0.55%; P=0.04) and PPG (−2.6 mmol/L; P=0.0009) from baseline to end point when compared to placebo.</p> <p>Secondary: FPG decreased in the miglitol group and was almost unchanged from baseline with placebo, the difference was not significant (P=0.10).</p> <p>Fasting insulin levels were unchanged for both groups throughout the study, the difference was not significant (P=0.79).</p> <p>Postprandial insulin decreased from baseline to end point, but the difference between the groups was not significant (P=0.26).</p> <p>Postprandial TG decreased slightly in the miglitol group and remained unchanged in the placebo group, the difference was not significant (P=0.47).</p>
<p>Pantalone et al.¹⁰⁸ (2012)</p> <p>glimepiride and metformin vs glipizide and metformin</p>	<p>RETRO</p> <p>Patients ≥18 years with type 2 diabetes who had a prescription for glyburide (glibenclamide),</p>	<p>N=7,320</p> <p>Median follow-up 2.4 years</p>	<p>Primary: Overall mortality</p> <p>Secondary: Not reported</p>	<p>Primary: No difference in overall mortality risk was found among the different combinations of sulfonylureas and metformin. Post-propensity adjustment results were: glimepiride and metformin vs glipizide and metformin (HR, 1.03; 95% CI, 0.89 to 1.20; P=0.69); glimepiride and metformin vs glyburide and metformin (HR, 1.08; 95% CI, 0.90 to 1.30; P=0.42); and glipizide and metformin vs glyburide and metformin (HR, 1.05; 95% CI, 0.95 to 1.15; P=0.34).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>glimepiride and metformin vs glyburide (glibenclamide) and metformin</p> <p>glipizide and metformin vs glyburide (glibenclamide) and metformin</p>	<p>glipizide, or glimepiride, in combination with metformin</p>			<p>Secondary: Not reported</p>
<p>Kabadi et al.¹⁰⁹ (2003)</p> <p>Tolazamide 1 gram daily plus premixed 70% NPH and 30% regular insulin daily</p> <p>vs</p> <p>glyburide 20 mg daily plus premixed 70% NPH and 30% regular insulin daily</p> <p>vs</p> <p>glipizide XL plus premixed 70% NPH and 30% regular insulin daily</p>	<p>PC, RCT</p> <p>Patients with type 2 diabetes mellitus with a lapse of glycemic control, established by documentation of HbA_{1c} >7.4% on ≥2 occasions at an interval of ≥3 months in each patient while taking oral sulfonylureas consisting of one of these drugs in the maximum recommended daily dose: tolazamide 1 g daily, glyburide 20 mg daily, glipizide XL 20 mg daily, or glimepiride 8 mg daily</p>	<p>N=40</p> <p>7 months</p>	<p>Primary: Changes in body weight, HbA_{1c}, and fasting C-peptide concentrations</p> <p>Secondary: Changes in daily insulin dose and the number of hypoglycemic episodes confirmed by finger stick blood glucose <60 mg/ dL</p>	<p>Primary: Changes in body weight were 2.5±0.8 kg for the tolazamide group, 2.6±1.0 kg for the glyburide group, 2.4±0.9 kg for the glipizide XL group, and 2.2±0.7 kg for the glimepiride group, all were significant compared to placebo (P<0.01) after the addition of insulin.</p> <p>All groups achieved optimal glycemic control as expressed by HbA_{1c} <7.4%, 1% above the highest normal level of 6.4% in our laboratory as recommended by the American Diabetes Association after the addition of insulin. HbA_{1c} was 6.8±0.4% for tolazamide, 6.9±0.4% for glyburide, 6.7±0.4% for glipizide XL, 6.7±0.3% for glimepiride, and 7.0±0.3% for placebo.</p> <p>C-peptide levels decreased in all groups. The reduction in the C-peptide level was significantly greater (P<0.05) in the placebo group compared to the sulfonylurea groups. There were no significant differences among the sulfonylurea groups.</p> <p>Secondary: Patients receiving sulfonylureas required a significantly lower (P<0.01) daily insulin dose, as well as dose per kilogram of body weight in comparison to patients receiving placebo (P<0.01).</p> <p>The daily insulin dose and units per kilogram of body weight was significantly lower (P<0.05) in patients receiving glimepiride in comparison to those receiving tolazamide, glyburide, or glipizide XL.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>glimepiride 8 mg daily plus premixed 70% NPH and 30% regular insulin daily</p> <p>vs</p> <p>placebo plus premixed 70% NPH and 30% regular insulin daily</p>				<p>The number of hypoglycemic episodes during the last four weeks of the study were significantly lower in the sulfonylurea groups as compared to the placebo group (P<0.01). The differences among the individual sulfonylurea groups were not significantly different.</p>
<p>Ligvay et al.¹¹⁰ (2009)</p> <p>Pioglitazone 15 to 45 mg QD plus glyburide 1.25 mg BID</p> <p>vs</p> <p>insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily</p> <p>All patients were receiving metformin 1,000</p>	<p>RCT, OL</p> <p>Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve</p>	<p>N=58</p> <p>36 months</p>	<p>Primary: HbA_{1c}, rate of treatment failures (defined as HbA_{1c} >8.0%), hypoglycemia, weight gain, compliance, QOL, and patient satisfaction</p> <p>Secondary: Not reported</p>	<p>Primary: After 36 months, HbA_{1c} was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26).</p> <p>The percentage of patients achieving HbA_{1c} <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the HbA_{1c} goal at the end of 36 months.</p> <p>Three patients in each group reached the “treatment failure” end point.</p> <p>The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53).</p> <p>In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) versus 3.36 kg (-0.47 to 7.20; P=0.04).</p> <p>Compliance was high throughout the trial: 93% in the insulin-treated group</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID Doses of medications could be titrated at the investigator's discretion.				and 90% in the triple oral group. There were differences between the groups for any of the 12 QoL domains evaluated. All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization. Secondary: Not reported
Bayraktar et al. ¹¹¹ (1996) Sulfonylurea and acarbose 50 to 100 mg TID vs sulfonylurea and metformin 500 mg TID	RCT, XO Patients from 30 to 63 years of age with type 2 diabetes for 2 to 20 years, HbA _{1c} >8.5%, FPG >7.7 mmol/L, or a PPG >10 mmol/L on maximum doses of gliclazide† (240 mg daily)	N=18 20 weeks	Primary: Changes in FBG, PPG, HbA _{1c} , TGs, cholesterol, fibrinogen, insulin levels, and C-peptide levels from baseline Secondary: Not reported	Primary: Mean FPG, PPG, and HbA _{1c} decreased at the end of each combination treatment period as compared with baseline levels (P<0.05). PPG level in the acarbose group was lower than the level achieved by the group using metformin (P<0.05). Each saw a statistically significant decrease between pre- and posttreatment two-hour postprandial blood glucose levels (−5.3±0.4 for acarbose vs −2.9±0.3 for metformin; P<0.05). There were small reductions in fibrinogen, insulin, and C-peptide levels in each group, but the differences were not statistically significant. Cholesterol levels remained unchanged with both treatment groups. Secondary: Not reported
Abbasi et al. ¹¹² (2004) Sulfonylurea (existing therapy) and metformin 500 to 1,000 mg BID vs	RCT Patients with type 2 diabetes with relatively poor glycemic control with FPG >9.5 mmol/L on dietary therapy alone or	N=31 12 weeks	Primary: Changes in fasting glucose, HbA _{1c} , lipid concentrations Secondary: Not reported	Primary: FPG decreased to a similar degree with diet therapy (metformin) (12.45±0.48 vs 9.46±0.47 mmol/L; P<0.001) and combined sulfonylurea plus metformin (14.09±0.51 vs 10.57±0.85 mmol/L; P=0.001). The changes in the diet therapy (metformin) group compared to the combined sulfonylurea plus metformin group was not significant (P=0.58). Changes in fasting HbA _{1c} from baseline were significant for diet therapy (metformin) (P<0.001) and combined sulfonylurea plus metformin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>dietary therapy and metformin 500 to 1,000 mg BID</p>	<p>sulfonylurea monotherapy, BMI <40 kg/m², and no apparent cardiovascular disease</p>			<p>(P<0.002). The changes were not significant when compared to each other (P=0.30).</p> <p>Fasting TC, TG, HDL-C, and LDL-C did not change significantly in either treatment group (P=0.64, P=0.34, P=0.48, and P=0.85, respectively) for diet therapy (metformin) compared to combined sulfonylurea plus metformin.</p> <p>Fasting remnant lipoprotein cholesterol concentrations were significantly lower in the diet therapy (metformin) group as compared to baseline (0.43±0.09 vs 0.34±0.07 mmol/L; P=0.02). The changes were not significant for diet therapy (metformin) compared to combined sulfonylurea plus metformin (P=0.06).</p> <p>Concentrations of FFA and remnant lipoprotein cholesterol concentrations were lower to a similar degree in both groups, whereas day long plasma insulin concentrations were unchanged. Changes in LDL particle diameter and percent of small dense LDL particles between the groups were not significant at end point (P=0.28 and P=0.73, respectively).</p> <p>Secondary: Not reported</p>
<p>Seufert et al.¹¹³ (2008)</p> <p><u>Study 1</u> Gliclazide† 80 to 320 mg daily and metformin (existing therapy)</p> <p>vs</p> <p>pioglitazone 15 to 45 mg QD and metformin (existing therapy)</p>	<p>2 MC, RCT</p> <p>Patients 35 to 75 years of age with type 2 diabetes who were inadequately controlled on either metformin or sulfonylurea monotherapy (HbA_{1c} 7.5 to 11.0%), and fasting C-peptide >1.5 ng/mL)</p>	<p>N=1,269</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline, FPG, glucose excursions using three-hour oral glucose tolerance test and insulin sensitivity</p> <p>Secondary: Not reported</p>	<p>Primary: <u>Study 1</u> The mean change in HbA_{1c} from baseline to week 104 was -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20).</p> <p>The mean change in FPG from baseline to week 104 was -1.8 mmol/L with pioglitazone and metformin compared to -1.1 mmol/L with gliclazide and metformin (P<0.001).</p> <p>Pioglitazone therapy in patients failing metformin therapy achieved decreases in glucose excursions at the end of the 2-year treatment period. This effect was not seen in the patients receiving gliclazide for two years as add-on therapy to failing metformin.</p> <p>Insulin sensitivity increased when pioglitazone was added to metformin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p><u>Study 2</u> Sulfonylurea (existing therapy) and pioglitazone 15 to 45 mg QD</p> <p>vs</p> <p>sulfonylurea (existing therapy) and metformin 850 to 2,550 mg daily</p>				<p>therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001).</p> <p><u>Study 2</u> The mean change in HbA_{1c} from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173).</p> <p>The mean change in FPG from baseline to week 104 was -2.0 mmol/L with pioglitazone and sulfonylurea compared to -1.9 mmol/L with metformin and sulfonylurea (P=0.506).</p> <p>The addition of pioglitazone to failing sulfonylurea therapy for two years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment.</p> <p>Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to sulfonylurea (P=0.581 between treatments).</p> <p>Secondary: Not reported</p>
<p>Matthews et al.¹¹⁴ (2005)</p> <p>Gliclazide† 80 to 320 mg QD and metformin (existing therapy)</p> <p>vs</p> <p>pioglitazone 15 to 45 mg QD and metformin (existing therapy)</p>	<p>DB, RCT</p> <p>Patients with type 2 diabetes that was poorly controlled (HbA_{1c} 7.5 to 11.0%) with metformin monotherapy</p>	<p>N=630</p> <p>12 months</p>	<p>Primary: Effect on HbA_{1c}</p> <p>Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide</p>	<p>Primary: Similar reductions in HbA_{1c} were observed in pioglitazone- (-0.99%) and gliclazide-treated groups (-1.01%; P=0.837).</p> <p>Secondary: Similar reductions in FPG were observed in pioglitazone- (-2.1 mmol/L) and gliclazide- (-1.6 mmol/L) treated groups (P=0.506).</p> <p>Gliclazide significantly reduced LDL-C compared to pioglitazone (-4.2 vs +10.4 mg/dL; P=0.001).</p> <p>Pioglitazone significantly reduced TG (-53.1 vs -19.5 mg/dL; P<0.001) and increased HDL-C (6.9 vs no change; P<0.001) compared to gliclazide.</p>
<p>Charbonnel et</p>	<p>DB, RCT</p>	<p>N=630</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>al.¹¹⁵ (2005)</p> <p>Gliclazide† 80 to 320 mg QD and metformin (existing therapy)</p> <p>vs</p> <p>pioglitazone 15 to 45 mg QD and metformin (existing therapy)</p>	<p>Patients with type 2 diabetes that was poorly controlled (HbA_{1c} 7.5 to 11.0%) with metformin monotherapy</p>	<p>24 months</p>	<p>Effect on HbA_{1c}</p> <p>Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide</p>	<p>Similar reductions in HbA_{1c} were observed with pioglitazone add-on therapy (−0.89%) and with gliclazide add-on therapy (−0.77%; P=0.200) after 2 years.</p> <p>Secondary: Significant reductions in FPG were observed with pioglitazone add-on therapy (−1.8 mmol/L) compared to gliclazide add-on therapy (−1.1 mmol/L; P<0.001) after two years.</p> <p>Gliclazide add-on therapy had significantly reduced LDL-C compared to pioglitazone add-on therapy (−6 vs +2 mg/dL; P<0.001).</p> <p>Pioglitazone add-on therapy significantly reduced TG (−23 vs −7 mg/dL; P<0.001) and increased HDL-C (22 vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy.</p> <p>No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported.</p> <p>Less weight gain was observed with gliclazide add-on therapy to metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg).</p>
<p>Hanefeld et al.¹¹⁶ (2004)</p> <p>Sulfonylurea (existing therapy) and pioglitazone 15 to 45 mg QD</p> <p>vs</p> <p>sulfonylurea (existing therapy) and metformin 850 to 2,250 mg</p>	<p>DB, MC, PG, RCT</p> <p>Patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy</p>	<p>N=639</p> <p>12 months</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: FPG, fasting plasma insulin, lipids, urinary albumin and creatinine (to determine albumin-to-creatinine ratio)</p>	<p>Primary: HbA_{1c} was reduced by 1.20 and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments).</p> <p>Secondary: FPG (P=0.528) and fasting plasma insulin (P=0.199) were also reduced but the between-treatment differences were not statistically significant.</p> <p>Pioglitazone addition to sulfonylurea significantly reduced TG (−16 vs −9%; P=0.008) and increased HDL-C (14 vs 8%; P<0.001) compared with metformin addition.</p> <p>LD-C was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001).</p> <p>Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group and increased 2% in the metformin group (P=0.017). Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group.
Comaschi et al. ¹¹⁷ (2008) Metformin/ glibenclamide* fixed dose combination 400/2.5 mg 1 to 3 tablets daily vs Pioglitazone 15 to 30 mg QD as add- on to existing oral hypoglycemic therapy (either metformin or sulfonylurea)	MC, OL, PG, RCT Patients aged ≥35 years with type 2 diabetes who had received treatment with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months before study entry, HbA _{1c} 7.5 to 11.0%, and fasting C- peptide >0.33 nmol/L	N=250 6 months	Primary: Change in HbA _{1c} from baseline to six months Secondary: Change in lipid profiles after six months of treatment	Primary: Pioglitazone-based and fixed-dose metformin/glibenclamide resulted in similar reductions in HbA _{1c} (-1.11 vs -1.29%, respectively; P=0.192) and FPG (-2.13 vs -1.81 mmol/L, respectively; P=0.370). Secondary: No changes in TC were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479). The addition of pioglitazone to metformin or a sulfonylurea led to a slight increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001). There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.01 mmol/L; P=0.677). There was no significant change in LDL-C in patients treated with pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425) There was a significant reduction in TGs with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045).
Home et al. ¹¹⁸ (2007) Sulfonylurea plus metformin vs	MC, OL, RCT Patients with type 2 diabetes between 40 and 75 years of age, BMI >25.0 kg/m ² , HbA _{1c} 7.1 to 9.0% while receiving	N=4,447 (n=1,117 rosiglitazone plus metformin; n=1,103 rosiglitazone plus	Primary: Hospitalization or death from cardiovascular causes Secondary: Death from	Primary: For adjudicated primary end points (hospitalization or death from cardiovascular causes), the HR was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone plus either metformin or a sulfonylurea	maximum permitted or tolerated doses of metformin or a sulfonylurea; exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension	sulfonylurea ; n=2,227 metformin plus sulfonylurea) Mean follow-up 3.75 years for the unplanned interim analyses (study was designed to be 6 years)	cardiovascular causes and from any cause, MI, congestive heart failure, and composite of death from cardiovascular causes, MI and stroke	<p>Secondary: There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI.</p> <p>Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006).</p>
Home et al. ¹¹⁹ (2009) Sulfonylurea plus metformin vs rosiglitazone plus either metformin or a sulfonylurea	MC, OL, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m ² , on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA _{1c} 7.0 to 9.0%)	N=4,458 5.5 years (mean follow-up)	<p>Primary: Time to first cardiovascular hospitalization or cardiovascular death</p> <p>Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke</p>	<p>Primary: The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 patients receiving rosiglitazone and active control, respectively (HR, 0.99; 95% CI, 0.85 to 1.16; P=0.93).</p> <p>Secondary: There was no significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR, 0.84; 95% CI, 0.59 to 1.18; P=0.32), all-cause mortality (HR, 0.86; 95% CI, 0.68 to 1.08; P=0.19), MI (HR, 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR, 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of cardiovascular death, MI, or stroke (HR, 0.93; 95% CI, 0.74 to 1.15; P=0.50).</p> <p>Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR, 2.10; 95% CI, 1.35 to 3.27; P=0.0010).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>There were no serious adverse event reports of macular edema. The incidence of bone fractures was higher with rosiglitazone compared to active control (RR, 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR, 1.82; 95% CI, 1.37 to 2.41 vs RR, 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on rosiglitazone was primarily in the upper limb (RR, 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR, 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures.</p>
<p>Home et al.¹²⁰ (2007)</p> <p>Sulfonylurea plus metformin</p> <p>vs</p> <p>rosiglitazone plus either metformin or a sulfonylurea</p>	<p>MC, OL, PG, RCT</p> <p>Patients 40 to 75 years of age with type 2 diabetes and BMI \geq25 kg/m², on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)</p>	<p>N=1,122</p> <p>18 months</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, serum lipids, HOMA basal insulin sensitivity and islet β-cell function (HOMA %β), body weight, inflammatory/thrombotic markers, CRP</p>	<p>Primary: At 18 months, HbA_{1c} reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference, 0.07%; 95% CI, -0.09 to 0.23; P value not significant), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference, 0.06%; 95% CI, -0.09 to 0.20; P value not significant).</p> <p>Secondary: Differences in FPG were not significant at 18 months (rosiglitazone vs sulfonylurea, -0.36 mmol/L; P=0.062 and rosiglitazone vs metformin, -0.34 mmol/L; P=0.089).</p> <p>Rosiglitazone increased TC (P\leq0.001) and LDL-C (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared to the control. An increase in HDL-C and TG was observed with rosiglitazone compared to sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001, 0.40 vs 0.15 mmol/L; P=0.016, respectively), but not with metformin (P value not significant for both).</p> <p>HOMA-estimated basal insulin sensitivity was substantially increased with rosiglitazone compared to the respective controls (P<0.001 for both). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, to a similar extent (P value not significant).</p> <p>Rosiglitazone was associated with a significant increase in body weight</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>compared to metformin (P<0.001) and a sulfonylurea (P=0.003).</p> <p>At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to sulfonylureas (-5.7 vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P value not significant).</p> <p>There was a significant reduction in CRP with rosiglitazone compared to a sulfonylurea (P<0.001) and metformin (P=0.001).</p>
<p>Mahaffey et al.¹²¹ (2013) RECORD re-evaluation Metformin plus a sulfonylurea vs rosiglitazone plus either metformin or a sulfonylurea</p>	<p>RETRO Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m², on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)</p>	<p>N=4,458 5.5 years (mean follow-up)</p>	<p>Primary: Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke</p>	<p>Primary: For the primary end point (time to first occurrence of CV (or unknown cause) death, MI, or stroke) no statistically significant difference was observed between rosiglitazone and metformin/sulfonylurea using the original RECORD end point definitions (HR, 0.95; 95% CI, 0.78 to 1.17). For the primary end point, no meaningful difference between rosiglitazone and metformin/sulfonylurea was observed using the original RECORD end point definitions (HR, 0.95; 95% CI 0.78 to 1.17) or new FDA end point definitions (HR, 0.97; 95% CI, 0.79 to 1.18). Furthermore, these results are similar to results from the original RECORD study (HR, 0.93; 95% CI, 0.74 to 1.15). Secondary: The original RECORD study results and the Duke Clinical Research Institute clinical events classification results were also similar for the individual components of the composite end point. These findings and the additional sensitivity analyses performed support the original RECORD results and suggest that when using essentially the same data, the observations were not affected by different clinical events classification processes, physician adjudicators, or end point definitions.</p>
<p>Komajda et al.¹²² (2008) Sulfonylurea plus metformin vs</p>	<p>RCT, MC, OL, (RECORD) Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m², on</p>	<p>N=668 12 months</p>	<p>Primary: Change from baseline in 24-hour ambulatory BP at six months and 12 months</p>	<p>Primary: For patients receiving rosiglitazone and a sulfonylurea, the reduction in 24-hour SBP was greater at six months (-3.8 mm Hg) and 12 months (-3.8 mm Hg) than with metformin and sulfonylurea therapy (-1.2 mm Hg and -1.3 mm Hg, respectively; six months, P=0.015; 12 months, P=0.031). Reductions in 24-hour DBP were greater at six months and 12 months for</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone plus either metformin or a sulfonylurea	maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA _{1c} 7.0 to 9.0%)		Secondary: Not reported	<p>patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mm Hg) compared to metformin and sulfonylurea (-0.4 mm Hg and -0.6 mm Hg; both P<0.001).</p> <p>At 12 months, the reduction in 24-hour SBP was greater for rosiglitazone and metformin (-4.9 mm Hg) than for metformin and sulfonylurea (-2.2 mm Hg; P=0.016).</p> <p>At 12 months, the reduction in DBP was greater for rosiglitazone and metformin (-3.8 mm Hg) than for metformin and sulfonylurea (-1.7 mm Hg; P=0.003).</p> <p>At six months, the reductions in SBP and DBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (SBP; P=not significant; DBP; P=0.049).</p> <p>Secondary: Not reported</p>
<p>Hamann et al.¹²³ (2008)</p> <p>Glibenclamide* 5 mg or gliclazide† 80 mg and metformin 2,000 mg daily (SU+MET)</p> <p>vs</p> <p>rosiglitazone/metformin FDC 4 mg/2,000 mg daily (RSG+MET)</p>	<p>RCT, DB, PG</p> <p>Overweight patients (BMI ≥25 kg/m²) with type 2 diabetes, HbA_{1c} 7.0 to 10.0%, who received metformin ≥850 mg/day for at least 8 weeks</p>	<p>N=596</p> <p>52 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 52</p> <p>Secondary: Change in FPG, β-cell function, insulin resistance, hypoglycemia, BP</p>	<p>Primary: At week 52, mean change in HbA_{1c} from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25).</p> <p>Secondary: Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095).</p> <p>The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs 0.055 HbA_{1c}%/year, respectively; P=0.0002).</p> <p>Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001).</p> <p>Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001).</p> <p>After 52 weeks, 24-hour diastolic and systolic ambulatory BP were reduced</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ambulatory BP (-2.9 mm Hg; P=0.0013), but not for systolic ambulatory BP (-2.6 mm Hg; P=0.0549).
Duckworth et al. ¹²⁴ (2003) Glyburide/ metformin	RETRO Patients 18 to 80 years of age with type 2 diabetes were eligible if they had received a combination product with glyburide and metformin for ≥90 days and had been treated with glipizide or glyburide plus metformin for ≥6 months prior to switching to the combination product of glyburide/ metformin	N=72 196 days (mean follow-up)	Primary: Changes in HbA _{1c} , lipid parameters, weight Secondary: Not reported	Primary: The mean baseline HbA _{1c} in the total population was 8.3±1.7%. The mean reduction in HbA _{1c} was 0.6% (P=0.002) with a mean follow-up of 196 days after the initiation of glyburide/metformin. The mean daily doses of glyburide and metformin at baseline and at final follow-up were 17.2 and 1,607 mg and 14.7 and 1,750 mg, respectively. The greatest decrease in HbA _{1c} was observed in patients with a baseline HbA _{1c} ≥8.0% (n=37). This group had a mean reduction of HbA _{1c} of 1.3% (P=0.0002) with similar doses of glyburide (14.7 vs 16.9 mg; P=0.077) and metformin (1,743 vs 1,624 mg; P=0.11) in both treatment periods. There were no significant changes in TC, HDL-C, LDL-C, or TG from baseline. There were no significant changes in body weight from a baseline level of 104.3 kg to the last follow-up weight of 104.0 kg (P=0.0645). There were no significant differences in patient adherence to the regimen (92.4% before vs 90.9% after). Secondary: Not reported
Blonde et al. ¹²⁵ (2003) Glyburide coadministered with metformin vs glyburide/ metformin	RETRO Patients with type 2 diabetes new to the combination product glyburide/ metformin or glyburide coadministered with metformin between August 2000 and	N=1,421 ~ 6 month (follow-up period)	Primary: Change in HbA _{1c} Secondary: Not reported	Primary: The mean HbA _{1c} for the two groups at baseline were similar, 9.1% for the combination product and 9.2% for the individual agents coadministered. During the follow-up period, patients taking the combination product had a lower mean daily dose of glyburide and metformin than patients receiving the individual agents coadministered regardless of baseline HbA _{1c} . Fifty-six percent of patients in the combination group achieved an HbA _{1c} <7.0% compared to 31.2% of patients receiving the individual agents coadministered. The mean HbA _{1c} decrease from baseline in the combination group was -2.02% and -1.49% when the individual agents were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	July 2001 and had HbA _{1c} levels at baseline within 79 to 194 days of initiating combination therapy			<p>coadministered. The regression results indicated that patients taking the combination product had a significantly greater (P<0.0001) reduction in HbA_{1c} than patients receiving the individual agents coadministered.</p> <p>Patients receiving the combination product with baseline HbA_{1c} ≥8.0% experienced a significantly (P<0.0001) greater decrease in HbA_{1c} of 2.93% compared to 1.92% for the individual agents coadministered.</p> <p>For patients with baseline HbA_{1c} <8.0%, the difference between the HbA_{1c} responses remained significant. The reductions in HbA_{1c} were smaller for both the combination product and the individual agents coadministered (-0.54 and -0.23%; P=0.0017).</p> <p>Patients were more adherent with the combination product than the individual agents coadministered (84% days with drug supply vs 76% days with drug supply, respectively; P<0.0001). The mean decreases in HbA_{1c} were similar for those patients ≥80% adherent and <80% adherent for the combination product (2.12 vs 2.19%; P value not significant) and the individual agents coadministered (1.47 vs 1.24%; P value not significant).</p> <p>Secondary: Not reported</p>
<p>Johnson et al.¹²⁶ (2005)</p> <p>Sulfonylurea monotherapy</p> <p>vs</p> <p>metformin monotherapy</p> <p>vs</p> <p>combination therapy of</p>	<p>RETRO</p> <p>Patients ≥30 years of age who were new users of oral antidiabetic drugs (sulfonylurea monotherapy, metformin monotherapy, or combination therapy of sulfonylureas and metformin)</p>	<p>N=4,124</p> <p>N=2,138 sulfonylurea monotherapy</p> <p>N=923 metformin monotherapy</p> <p>N=1,081 combination therapy</p>	<p>Primary: Composite end point of fatal or nonfatal cardiovascular related events</p> <p>Secondary: Not reported</p>	<p>Primary: A total of 381 patients died from cardiovascular causes and 715 were hospitalized at least once for cardiovascular reasons. Patients in the metformin monotherapy group had the lowest nonfatal hospitalization rate for cardiovascular causes (53.7 hospitalizations per 1,000 person years) compared to sulfonylurea monotherapy patients (75.3 per 1,000 person years; P<0.05) and compared to combination therapy patients (90.2 per 1,000 person years; P<0.05). Nonfatal cardiovascular related hospitalization rates were similar for sulfonylurea monotherapy patients and combination therapy patients (P=0.08).</p> <p>Metformin monotherapy was associated with a lower risk of the composite end point (adjusted HR, 0.81; 95% CI, 0.68 to 0.97) as compared to sulfonylurea monotherapy.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulfonylureas and metformin		Duration not reported		Cardiovascular hospitalizations were similar for sulfonylurea monotherapy and combination therapy (P=0.32). Secondary: Not reported
Swinnen et al. ¹²⁷ (2010) Continuation of secretagogues (sulfonylureas or meglitinides) vs discontinuation of secretagogues (sulfonylureas or meglitinides) All patients received existing metformin regimens and initiated insulin therapy.	PRO Patients 40 to 75 years of age with type 2 diabetes, HbA _{1c} 7.0 to 10.5% receiving oral glucose-lowering drugs	N=865 24 weeks	Primary: Change in HbA _{1c} Secondary: Hypoglycemia, body weight, insulin dose	Primary: In patients continuing secretagogue treatment, HbA _{1c} decreased to 7.0±0.8% at week 12 compared to 7.4±0.9% in patients discontinuing their secretagogues. Endpoint HbA _{1c} level was 7.2±0.9% in both treatment groups. The difference in mean HbA _{1c} reduction during the trial was not significant (-1.59±1.08% for patients continuing secretagogues and -1.30±1.14% for patients discontinuing secretagogues; P=0.382). Secondary: Compared to patients who discontinued secretagogues, patients who continued secretagogues experienced significantly more hypoglycemia (40.0 vs 24.5%; P<0.001) and gained significantly more weight (1.44±3.04 vs 0.43±3.00 kg; P<0.001). End of trial insulin doses, were significantly lower in patients who continued secretagogues compared to patients who discontinued secretagogues (P<0.001).
Hollander et al. ¹²⁸ (2015) Insulin glargine+ one oral antidiabetes drug (metformin or sulfonylurea) wherein previous TZD therapy was dropped and	MC, OL, RCT Type 2 diabetes patients 18 to 79 years of age with a HbA _{1c} of 7.5 to 12.0% despite ≥3 months of treatment with a TZD plus metformin or a sulfonylurea	N=337 48 weeks	Primary: Change in HbA _{1c} Secondary: Changes in FPG, weight, BMI, and serum lipid profile	Primary: Substitution of insulin glargine for a TZD and addition of a third OAD resulted in an adjusted mean change in HbA _{1c} from baseline of -1.66% and -1.86%, respectively (adjusted mean difference 0.20; 95% CI, -0.11 to 0.51). The upper limit of the 95% CI for the difference in the adjusted mean changes from baseline to endpoint for HbA _{1c} was 0.51%; therefore, the primary efficacy analysis did not demonstrate equivalent glycemic control during treatment with GLAR + 1 OAD and 3OAD as measured by HbA _{1c} levels. In patients originally taking sulfonylurea, there was a significantly greater reduction in HbA _{1c} in those adding metformin to TZD and sulfonylurea versus those switching the TZD for GLAR + SU at weeks 12,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>replaced with insulin glargine (GLAR +1 OAD)</p> <p>vs</p> <p>three oral antidiabetes drugs (3OAD) wherein patients receiving TZD and metformin received add-on sulfonylurea (glyburide) and patients receiving TZD and sulfonylurea received add-on metformin (3OAD)</p>				<p>24, and 48.</p> <p>Secondary: Adjusted mean FPG at baseline was similar between the two treatment arms (GLAR + 1 OAD 193.0 mg/dL vs 3OAD 199.5 mg/dL; P=0.4299). FPG reduced significantly from baseline to endpoint (P<0.0001 for both arms).</p> <p>Weight gain was observed in both treatment arms at each study visit and at endpoint. At each visit, patients in the GLAR + 1 OAD arm gained less weight than those in the 3OAD arm; this difference was significant at week 12 (P=0.0035). A similar pattern was observed for BMI.</p> <p>Overall, insulin glargine + metformin was as effective as 3OAD in achieving glycemic control but with greater improvements in lipid parameters, less weight gain, and lower hypoglycemia rates.</p>
<p>Kheirbek et al.¹²⁹ (2013)</p> <p>Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone,</p>	<p>OS, RETRO</p> <p>Veterans with diabetes cared for at a Veterans Administration Capital area medical center</p>	<p>N=17,773</p> <p>Variable duration</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Not reported</p>	<p>Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use				
Mearns et al. ¹³⁰ (2015) Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)	Network MA (62 RCTs) Patients with inadequately controlled type 2 diabetes on metformin alone	N=32,185 3 to 12 months	Primary: Changes in HbA _{1c} , body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	Primary: All agents significantly reduced HbA _{1c} vs placebo; although not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported
Gestational Diabetes				
Moore et al. ¹³¹ (2010) Glyburide 2.5 to 10 mg BID vs metformin 500 to 2,000 mg daily	DB, PG, RCT Women with gestational diabetes between 11 and 33 weeks gestation at the time of randomization	N=149 Variable duration	Primary: Glycemic control Secondary: Medication failure rate, macrosomia, admission to the neonatal intensive care unit, five-minute Apgar	Primary: There was no difference between the glyburide or metformin groups in mean fasting (P=0.23) or two-hour PPG concentrations (post-breakfast, P=0.15; post-lunch, P=0.28; post-dinner, P=0.32). Secondary: Twenty-six patients (34.7%) in the metformin group and 12 patients (16.2%) in the glyburide group did not meet glycemic goals and required insulin therapy (P=0.01). The failure rate of metformin was 2.1 times higher than the failure rate of glyburide (95% CI, 1.2 to 3.9; OR, 2.7).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(divided doses)</p> <p>Insulin was started in treatment failures and oral medication was discontinued.</p>			<p>score <7, birth trauma, preeclampsia, maternal and neonatal hypoglycemia, and route of delivery</p>	<p>Macrosomia occurred in 5.4% of patients in the glyburide group and 1.3% of patients in the metformin group (P=0.20). The mean birth weight of babies in the metformin group was smaller than the mean birth weight of babies in the glyburide group (P=0.02). Other neonatal outcomes did not differ between the two groups.</p> <p>There were four neonatal intensive care unit admissions in the metformin group and one neonatal intensive care unit admission in the glyburide group (P=0.37). There were no five-minute Apgar scores <7 in either group. There was one shoulder dystocia in the glyburide group and one third-degree tear in the metformin group (P=0.49).</p> <p>The incidence of maternal hypoglycemia and preeclampsia was not different between the two treatment groups (P=0.56 and P>0.50, respectively). One infant in the metformin group experienced hypoglycemia with blood glucose less than 40 mg/dL.</p> <p>Excluding elective repeat cesarean deliveries, there were 11 cesarean deliveries in the metformin group compared with two cesarean deliveries in the glyburide group (P=0.02).</p>
<p>Mirzamoradi et al.¹³² (2015)</p> <p>Glyburide vs insulin</p>	<p>RCT</p> <p>Pregnant women 18 to 45 years of age with singleton pregnancies and in week 24 to 36 of gestation with gestational diabetes</p>	<p>N=96</p> <p>Variable duration</p>	<p>Primary: Glycemic index control</p> <p>Secondary: Fetal and maternal outcome, adverse events</p>	<p>Primary: Time from beginning the treatment to control the glycemic index was 28.30 ± 20.60 days in the insulin group and 22.56 ± 18.86 in the glyburide group. There was no statistically significant difference in time-tocontrol the blood glucose level in two studied group (P=0.17).</p> <p>Secondary: Time, between beginning the treatment of GDM and delivery, was 53.22 ± 28.96 days in the insulin group and 56.67 ± 30.47 in the glyburide group. There was no statistically significant difference between the time of treatment-to-delivery in two studied groups (P=0.57). The incidence of preeclampsia in the insulin group was higher than glyburide group (13.6 vs 8.1%) but this difference was not statistically significant (P=0.41). There was no statistically significant difference in birth weights between two groups (P=0.84). Eleven neonates needed NICU admission. All NICU</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Poolsup et al.¹³³ (2014)</p> <p>Pool A: metformin vs insulin</p> <p>Pool B: glyburide vs insulin</p>	<p>MA</p> <p>Women with gestational diabetes mellitus</p>	<p>N=2,151 (13 RCTs)</p> <p>Variable duration</p>	<p>Primary: Safety and efficacy of oral antidiabetic agents compared to insulin</p> <p>Secondary: Not reported</p>	<p>admissions were due to respiratory distress syndrome. There were no cases of hypoglycemia, hypocalcemia and polycythemia in both groups.</p> <p>Primary: <u>Pool A</u> There was a nonsignificant difference in the risk of macrosomia (RR, 0.93; 95% CI, 0.61 to 1.41) and large for gestational age (LGA) births (RR, 0.88; 95% CI, 0.70 to 1.12) between the two study groups. A significant increase in the risk of preterm births occurred in the metformin group as compared to insulin (RR, 1.51; 95% CI, 1.04 to 2.19; P=0.03). Rate of neonatal/perinatal mortality was very low in both groups and results remained statistically nonsignificant. Risk of shoulder dystocia, neonatal hypoglycemia, congenital abnormality, and small for gestational age (SGA) births tended to be lower with metformin but statistical significance was not achieved. A nonsignificant decrease in risk of caesarean section, pre-eclampsia, and labor induction was noticed with metformin compared to insulin. A significant decrease in the risk of gestational hypertension was observed in the metformin arm (RR, 0.54; 95% CI, 0.31 to 0.91; P=0.02). A significant decrease in PPG levels occurred (mean difference, -2.47 mg/dL; 95% CI, -4.00 to -0.94, P=0.002) in metformin group compared to insulin, while results were statistically nonsignificant between the two groups for FPG levels (mean difference, 0.74 mg/dL; 95% CI, -0.52 to -2.01).</p> <p><u>Pool B</u> Glyburide significantly increased the risk of macrosomia (RR, 3.07; 95% CI, 1.14 to 8.23; P=0.03) and neonatal hypoglycemia (RR, 2.30; 95% CI, 1.28 to 4.11; P=0.005) compared to insulin. There was no difference between glyburide and insulin with regard to risk for LGA births; statistically significant heterogeneity was detected for this outcome. There were no significant differences in the risk of preterm births, neonatal mortality, congenital abnormality, or SGA births for glyburide versus insulin. None of the maternal outcomes (caesarean section, pre-eclampsia, maternal hypoglycemia, glycemic levels) displayed a significant difference between glyburide and insulin. The effect estimate for fasting glucose levels (mean difference, 1.90 mg/dL; 95% CI, -0.38 to 4.18) and postprandial glucose levels (mean difference, 3.42 mg/dL; 95% CI, -1.17 to 8.02) favored the insulin group, but results remained nonsignificant.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported

*Synonym for glyburide.

†Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, TID=three times daily, XL=extended-release, XR=extended-release

Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OS=observational,

PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, SR=systematic review, XO=cross-over

Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4=dipeptidyl

peptidase-4, EQ-5D=EuroQol questionnaire, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein

cholesterol, HOMA-B=homeostasis model assessment-beta cell function, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HOMA-S=homeostasis model assessment-insulin

sensitivity, HR=hazard ratio, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral

protamine Hagedorn, NYHA=New York Heart Association, OR=odds ratio, PPAR=peroxisome proliferator-activated receptors, PPG=postprandial plasma glucose, QOL=quality of life, RR=relative risk,

SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione, WMD=weighted mean difference

Additional Evidence

Dose Simplification

Dezii et al. evaluated the differences in adherence and persistence with a once-daily extended-release formulation of glipizide gastrointestinal therapeutic system (GITS) and a twice-daily immediate-release formulation of glipizide. After one year of treatment, adherence rates were 60.5% in the once-daily group compared to 52.0% in the twice-daily group (P=0.027). Persistence rates were 44.4% in the once-daily group and 35.8% in the twice-daily group (P=0.016).¹³⁴ Donnan et al. evaluated the patterns and predictors of adherence in patients with type 2 diabetes receiving treatment with a single antidiabetic agent. Adherence was $\geq 90\%$ in 31.3% of the patients prescribed sulfonylureas and 33.9% of patients prescribed metformin. Patients with better adherence tended to be younger and had a shorter duration of diabetes. There were linear trends of poorer adherence with each increase in the daily number of tablets taken for both sulfonylurea (P=0.001) and metformin (P=0.074) indices. There were significant trends of decreasing adherence with the number of concomitant medications for the sulfonylurea group (P=0.0001) and metformin group (P=0.007).¹³⁵

Several retrospective database analyses have been conducted to assess adherence rates with various antidiabetic agents. Blonde et al. evaluated adherence rates in patients beginning treatment with a sulfonylurea and metformin. The first group consisted of patients who were receiving glyburide/metformin as a fixed-dose combination. The second group consisted of patients who were receiving the combination of glyburide and metformin as separate formulations. The investigators found that patients were more adherent with the fixed-dose combination product than with the agents administered in separate formulations (84% days with drug supply vs 76% days with drug supply, respectively, P<0.0001).¹²⁵ Duckworth et al. evaluated patients who were taking glipizide or glyburide in combination with metformin (administered as separate formulations) for at least six months. Patients were then switched to a fixed-dose combination of glyburide/metformin. The investigators found no significant difference in adherence (92.4% before vs 90.9% after the switch).¹²⁴ Melikian et al. evaluated adherence rates in newly treated or previously treated patients with type 2 diabetes. The investigators found no difference in adherence rates during the initial six months of therapy among patients who were receiving metformin monotherapy, glyburide monotherapy, or metformin and glyburide combination therapy (administered as separate formulations) as compared to patients who received a fixed-dose combination of glyburide/metformin. Significantly lower adherence rates were seen in patients receiving metformin monotherapy and glyburide monotherapy who had a second agent added at their regimen (54%; 95% CI, 0.52 to 0.55) compared to patients who were switched to a fixed-dose combination of glyburide/metformin (77%; 95% CI, 0.72 to 0.85).¹³⁶

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx

Relative Cost Index Scale	
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 10. Relative Cost of the Sulfonylureas

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Chlorpropamide	tablet	N/A	N/A	\$
Glimepiride	tablet	Amaryl ^{®*}	\$\$\$\$	\$
Glipizide	extended-release tablet, tablet	Glucotrol ^{®*} , Glucotrol XL ^{®*}	\$\$	\$
Glyburide	tablet	N/A	-\$\$\$\$\$	\$\$
Glyburide, micronized	tablet	Glynase ^{®*}	-\$\$\$\$\$	\$
Tolazamide	tablet	N/A	N/A	\$\$-\$\$\$\$
Tolbutamide	tablet	N/A	N/A	\$\$\$\$
Combination Products				
Glipizide and metformin*	tablet	N/A	N/A	\$\$
Glyburide, micronized and metformin	tablet	Glucovance ^{®*}	\$\$	\$

*Generic is available in at least one dosage form or strength.

N/A=Not available

X. Conclusions

The sulfonylureas are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹⁻⁷ All of the sulfonylureas are available in a generic formulation, including the fixed-dose combination products.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The sulfonylureas are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note that sulfonylureas are associated with weight gain and a greater risk of inducing hypoglycemia compared to other available antidiabetic medications. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/meglitinide, an SGLT2 inhibitor, pioglitazone, or a dipeptidyl peptidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one sulfonylurea over another is not stated.⁹⁻²¹

The sulfonylureas have been evaluated in numerous clinical trials.²⁴⁻¹³³ In monotherapy studies, glipizide and glyburide were found to be equally efficacious, regardless of the dosage form used.^{32-35,37,41} Several studies evaluated the efficacy of sulfonylureas in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.^{77-79,86-91,94} However, in studies that directly compared various dual therapy regimens, there were no differences in efficacy noted.^{102,113-117,120,123}

There is insufficient evidence to support that one brand sulfonylurea is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand sulfonylurea is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Amaryl[®] [package insert]. Bridgewater (NJ): sanofi-aventis U.S. LLC; 2016 Dec.
2. DiaBeta[®] [package insert]. Bridgewater (NJ): sanofi-aventis U.S. LLC; 2016 Jul.
3. Glucotrol XL[®] [package insert]. New York (NY): Roerig; 2015 Oct.
4. Glucotrol[®] [package insert]. New York (NY): Roerig; 2016 Aug.
5. Glucovance[®] [package insert]. Princeton (NJ): Bristol-Myers Squibb Company; 2013 Oct.
6. Glynase[®] PresTab[®] [package insert]. New York (NY): Pharmacia & Upjohn Company; 2015 May.
7. Daily Med [database on the internet]. Bethesda (MD): National Library of Medicine; 2017 [cited 2017 Mar]. Available at: <http://dailymed.nlm.nih.gov/dailymed/about.cfm>.
8. McCulloch DK. Sulfonylureas and meglitinides in the treatment of diabetes mellitus. In: UpToDate, Nathan DM and Mulder JE (Ed), UpToDate, Waltham, MA, 2017.
9. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2016;39(Suppl. 1):S1–S112.
10. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.
11. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015 Mar;58(3):429-42.
12. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.
13. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1:1-87.
14. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. Endocr Pract. 2016;22(1):84-113.
15. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
16. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
17. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
18. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131(2):364-382.
19. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.
20. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.
21. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care 2014;37(7):2034-2054.
22. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Mar]. Available from: <http://www.thomsonhc.com/>.
23. Facts and Comparisons[®] eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Mar 2017]. Available from: <http://online.factsandcomparisons.com>.

24. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998 Sep 12;352(9131):837-53.
25. Feinbock C, Luger A, Klingler A, et al. Prospective multicenter trial comparing the efficacy of, and compliance with, glimepiride or acarbose treatment in patients with type 2 diabetes not controlled with diet alone. *Diabetes Nutr Metab*. 2003;16(4):214-21.
26. Martin S, Kolb H, Beuth J, et al. Change in patients' body weight after 12 months of treatment with glimepiride or glibenclamide in type 2 diabetes: a multicenter retrospective cohort study. *Diabetologia*. 2003;46:1611-7.
27. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, et al. Liraglutide vs glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-weeks, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373:473-81.
28. Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycemic control and weight for two years as monotherapy compared to glimepiride in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011 Apr;13(4):348-56.
29. Bode BW, Testa MA, Magwire M, Hale PM, Hammer M, Blonde L, et al. Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. *Diabetes Obes Metab*. 2010;12:604-12.
30. Gottschalk M, Danne T, Vlajnic A, Cara JF. Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. *Diabetes Care*. 2007 Apr;30(4):790-4.
31. Hartley P, Shentu Y, Betz-Schiff P, et al. Efficacy and Tolerability of Sitagliptin Compared with Glimepiride in Elderly Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control: A Randomized, Double-Blind, Non-Inferiority Trial. *Drugs Aging*. 2015 Jun;32(6):469-76.
32. Go EH, Kyriakidou-Himonas M, Berelowitz M. Effects of glipizide GITS and glibenclamide on metabolic control, hepatic glucose production, and insulin secretion in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2004 May-Jun;20(3):225-31.
33. Birkeland KI, Furuseth K, Melander A, Mowinckel P, Vaaler S. Long-term randomized placebo-controlled double-blind therapeutic comparison of glipizide and glyburide. Glycemic control and insulin secretion during 15 months. *Diabetes Care*. 1994 Jan;17(1):45-9.
34. Burge MR, Schmitz-Fiorentino K, Fishertte C, Qualls CR, Schade DS. A prospective trial of risk factors for sulfonylurea-induced hypoglycemia in type 2 diabetes mellitus. *JAMA*. 1998 Jan 14;279(2):137-43.
35. Chung M, Kourides I, Canovatchel W, et al. Pharmacokinetics and pharmacodynamics of extended-release glipizide GITS compared with immediate-release glipizide in patients with type II diabetes mellitus. *J Clin Pharmacol*. 2002;42(6):651-7.
36. Hseih SH, Lin JD, Cheng HY et al. Sustained-release versus immediate-release glipizide for treatment of type 2 diabetes mellitus in Chinese patients: A randomized, double-blind, double-dummy, parallel-group, 12-week clinical study. *Clin Ther*. 2006;28(9):1318-26.
37. Kitabchi AE, Kaminska E, Fisher JN et al. Comparative efficacy and potency of long-term therapy with glipizide or glyburide in patients with type 2 diabetes mellitus. *Am J Med Sci*. 2000;319(3):143-8.
38. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care* 2013;36:1301-1311.
39. Scott R, Wu M, Sanchez M, Stein P. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. *Int J Clin Pract*. 2007 Jan;61(1):171-80.
40. Chan J, Scott R, Arjona Ferreira J, et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. *Diabetes Obes Metab* 2008;10:545-555.
41. Sami T, Kabadi UM, Moshiri S. The effect on metabolic control of second-generation sulfonylurea drugs in patients with NIDDM after secondary failure to first generation agents. (non-insulin-dependent diabetes mellitus). *J Fam Pract*. 1996;43(4):370-4.
42. Hollander P, Schwartz S, Gatlin M, Haas SJ, Zheng H, Foley JE, et al. Importance of early insulin secretion comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. *Diabetes Care*. 2003;24(6):983-8.
43. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006 Dec 7;355(23):2427-43.
44. Giles T, Miller A, Elkayam U, et al. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. *J Card Fail* 2008;14:445-52.

45. Johnston PS, Lebovitz HE, Coniff RF, et al. Advantages of α -glucosidase inhibition as monotherapy in elderly type 2 diabetic patients. *J Clin Endocrinol Metab.* 1998;83(5):1515-22.
46. van de Laar FA, Lucassen PL, Kemp J, van de Lisdonk EH, van Weel C, Rutten GE. Is acarbose equivalent to tolbutamide as first treatment for newly diagnosed type 2 diabetes in general practice? A randomized controlled trial. *Diabetes Res Clin Pr.* 2004 Jan;63(1):57-65.
47. Sullivan D, Forder P, Simes J, Whiting M, Kritharides L, Merrifield A, et al. Associations between the use of metformin, sulphonylureas, or diet alone and cardiovascular outcomes in 6005 people with type 2 diabetes in the FIELD study. *Diabetes Research and Clinical Practice.* 2011;9:284-90.
48. Simpson SH, Majumdar SR, Tsuyuki RT, et al. Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. *CMAJ.* 2006;174(2):169-74.
49. Nichols GA, Gomez-Caminero A. Weight changes following the initiation of new anti-hyperglycemic therapies. *Diabetes Obes Metab.* 2007 Jan;9(1):96-102.
50. Gangji AS, Cukierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care.* 2007;30(2):389-94.
51. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann of Int Med.* 2007;147(96):386-400.
52. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract.* 2008 Feb;79(2):196-203.
53. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005 Jul 20;(3):CD002966.
54. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD006423. DOI: 10.1002/14651858.CD006423.pub2.
55. Frederich R, Alexander JH, Fiedorek FT, Donovan M, Berglund N, Harris S, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. *Postgrad Med.* 2010 May;122(3):16-27.
56. Singh S, Loke YK, Furberg CD. Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systemic review and meta-analysis. *Thorax.* 2011;66:383-8.
57. Louisa M, Takeuchi M, Nafrialdi, Setiabudy R. A meta-analysis on treatment effects of thiazolidinediones for type 2 diabetes mellitus in Asian populations. *Acta Med Indones.* 2011 Jan;43(1):39-52.
58. Mannucci E, Monami M, Lamanna C, Gensini GF, Marchionni N. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. *Diabetes Obes Metab.* 2008;10:1221-38.
59. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2006 Oct 18;(4):CD006060.
60. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. *Lancet.* 2007 Sep 29;370:1129-36.
61. Nagajothi N, Adigopula S, Balamuthusamy S, Velazquez-Cecena JL, Raghunathan K, Khraisat A, et al. Pioglitazone and the risk of myocardial infarction and other major adverse cardiac events: a meta-analysis of randomized, controlled trials. *Am J Ther.* 2008;15:506-11.
62. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA.* 2007 Sep 12;298(10):1180-8.
63. Karter AJ, Ahmed AT, Liu J, Moffet HH, Parker MM. Pioglitazone initiation and subsequent hospitalization for congestive heart failure. *Diabetic Med.* 2005 Aug;22:986-93.
64. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356(24):2457-71.
65. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA.* 2007 Sep 12;298(10):1189-95.
66. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2007 Jul 18;(3):CD006063.
67. Lopez-Alvarenga JC, Aguilar-Salinas CA, Velasco-Perez ML, et al. Acarbose vs bedtime NPH insulin in the treatment of secondary failures to sulphonylurea-metformin therapy in type 2 diabetes mellitus. *Diabetes Obes Metab.* 1999;1(1):29-35.
68. Yokoyama H, Sone H, Yamada D, Honjo J, Haneda M. Contribution of glimepiride to basal-prandial insulin therapy in patients with type 2 diabetes. *Diabetes Research and Clinical Practice.* 2011;91:148-53.

69. Dhindsa P, Davis KR, Donnelly R. Comparison of the micro- and macro-vascular effects of glimepiride and gliclazide in metformin-treated patients with type 2 diabetes: a double-blind, crossover study. *Br J Clin Pharmacol.* 2003;55(6):616-9.
70. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 2013;382(9896):941-950.
71. Derosa G, Putignano P, Bossi A, Bonaventura A, Querci F, Franzetti IG, et al. Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type diabetic patients. *European Journal of Pharmacology.* 2011;666:251-6.
72. Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet* 2012; 379(9833):2270-2278.
73. Forst T, Uhlig-Laske B, Ring A, Graefe-Mody U, Friedrich C, Herbach K, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled type 2 diabetes. *Diabet Med.* 2010;27:1409-19.
74. Yang W, Chen L, Ji Q, Liu X, Ma J, Tandon N, et al. Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial. *Diabetes, Obesity and Metabolism.* 2011;13:81-8.
75. Charbonnel B, Steinberg H, Eymard E, et al. Efficacy and safety over 26 weeks of an oral treatment strategy including sitagliptin compared with an injectable treatment strategy with liraglutide in patients with type 2 diabetes mellitus inadequately controlled on metformin: a randomised clinical trial. *Diabetologia* 2013; 56:1503–1511.
76. Chogtu B, Singh N, Chawla S, et al. Impact of glitazones on metabolic and haemodynamic parameters in patients with type 2 diabetes mellitus. *Singapore Med J* 2009;50:395-9.
77. Chou H, Palmer J, Jones A, et al. Initial treatment with fixed-dose combination rosiglitazone/glimepiride in patients with previously untreated type 2 diabetes. *Diabetes Obes Metab* 2008;10:626-37.
78. McCluskey D, Touger MS, Melis R, Schleusener DS, McCluskey D. Results of a randomized, double-blind, placebo-controlled study administering glimepiride to patients with type 2 diabetes mellitus inadequately controlled with rosiglitazone monotherapy. *Clin Ther.* 2004;26(11):1783-90.
79. Rosenstock J, Chou H, Matthaei S, et al. Potential benefits of early addition of rosiglitazone in combination with glimepiride in the treatment of type 2 diabetes. *Diabetes Obes Metab* 2008;10:862-73.
80. Scherthaner G, Durán-García S, Hanefeld M, et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). *Diabetes Obes Metab.* 2015 Jul;17(7):630-8.
81. Scherthaner G, Rosas-Guzmán J, Dotta F, et al. Treatment escalation options for patients with type 2 diabetes after failure of exenatide twice daily or glimepiride added to metformin: results from the prospective European Exenatide (EUREXA) study. *Diabetes Obes Metab.* 2015 Jul;17(7):689-98.
82. Bao YQ, Zhou J, Zhou M, Cheng UJ, Lu W, Pan XP, et al. Glipizide controlled-release tablets, with or without acarbose, improve glycemic variability in newly diagnosed type 2 diabetes. *Clinical and Experimental Pharmacology and Physiology.* 2010;37:564-8.
83. Rosenstock J, Wilson C, and Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. *Diabetes, Obesity and Metabolism* 2013;15(10):906–914.
84. Del Prato S, Camisasca R, Wilson C, Fleck P. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. *Diabetes Obes Metab.* 2014 Dec;16(12):1239-46.
85. Del Prato S, Nauck M, Durán-García S, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. *Diabetes Obes Metab.* 2015 Jun;17(6):581-90.
86. Goldstein BJ, Pans M, Rubin CJ. Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. *Clin Ther.* 2003;25(3):890-903.
87. Göke B, Gallwitz B, Eriksson JG, et al. Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. *Int J Clin Pract* 2013; 67(4):307–316. doi: 10.1111/ijcp.12119

88. Garber AJ, Larsen L, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab.* 2002;4(3):201-8.
89. Marre M, Howlett H, Lehertt P, et al. Improved glycemic control with metformin-glibenclamide combined tablet therapy (Glucovance®) in type 2 diabetic patients inadequately controlled on metformin. *Diabet Med.* 2002;19(8):673-80.
90. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med.* 1995 Aug;333(9):541-9.
91. Chien HH, Chang CT, Chu NF, et al. Effect of glyburide-metformin combination tablet in patients with type 2 diabetes. *J Chin Med Assoc* 2007;70:473-80.
92. Lewin A, Lipetz R, Wu J, Schwartz S. Comparison of extended-release metformin in combination with a sulfonylurea (glyburide) to sulfonylurea monotherapy in adult patients with type 2 diabetes: a multicenter, double-blind, randomized, controlled, phase III study. *Clin Ther.* 2007 May;29(5):844-55.
93. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IS, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. *Diabetes Care.* 2009;32:84-90.
94. Marre M, Shaw J, Brandle M, Bebakar WMW, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycemic and weight control compared to adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med.* 2009;26:268-78.
95. Chacra AR, Tan GH, Apanovitch A, et al. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. *Int J Clin Pract* 2009;63:1395-406.
96. Goke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I; D1680C00001 Investigators. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. *Int J Clin Pract.* 2010 Nov;64(12):1619-31.
97. Arechavaleta R, Seck T, Chen Y, KJ Krobot, EA O'Neill, L Duran, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes, Obesity and Metabolism.* 2011;13:160-8.
98. Srivastava A, Saxena GN, Keshwani P, Gupta R. Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone. *JAPI.* 2012 Mar;60:27-30.
99. Seck TL, Engel SS, Williams-Herman DE, Sisk CM, Golm GT, Wang H, et al. Sitagliptin more effectively achieves a composite endpoint for A1C reduction, lack of hypoglycemia and no body weight gain compared with glipizide. *Diabetes Research and Clinical Practice.* 2011;93:e15-7.
100. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab.* 2007 Sep;9(5):733-45.
101. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP; Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab.* 2007 Mar;9(2):194-205.
102. Schwarz SL, Gerich JE, Marcellari A, et al. Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naïve elderly patients with type 2 diabetes. *Diabetes Obes Metab.* 2008; 10(8): 652-60.
103. Derosa G, D'Angelo A, Fogari E, et al. Nateglinide and glibenclamide metabolic effects in naïve type 2 diabetic patients treated with metformin. *J Clin Pharm Ther* 2009;34: 13-23.
104. Gerich J, Raskin P, Jean-Louis L, et al. PRESERVE-β Two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. *Diabetes Care.* 2003;28(9):2093-9.
105. Wolffenbittel B, Landgraf R. A 1-year Multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care.* 1999;22(3):463-7.
106. Cesur M, Corapcioglu D, Gursoy A, Gonen S, Ozduman M, Emral R, et al. A comparison of glycemic effects of glimepiride, repaglinide, and insulin glargine in type 2 diabetes mellitus during Ramadan fasting. *Diabetes Res Clin Pract.* 2007 Feb;75(2):141-7.
107. Standl E, Schernthaner G, Rybka J, et al. Improved glycemic control with miglitol in inadequately-controlled type 2 diabetics. *Diabetes Res Clin Pr.* 2001;51(3):205-13.

108. Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with Type 2 diabetes receiving different combinations of sulfonylureas and metformin: a retrospective analysis. *Diabet Med.* 2012;29(8):1029-1035.
109. Kabadi MU, Kabadi U. Efficacy of sulfonylureas with insulin in type 2 diabetes mellitus. *Ann Pharmacother.* 2003;37(11):1572-6.
110. Ligvay I, Legendre J, Kaloyanova P, et al. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? *Diabetes Care* 2009;32:1789-95.
111. Bayraktar M, Van Thiel D, Adalar N. A comparison of acarbose versus metformin as an adjuvant therapy in sulfonylurea-treated NIDDM patients. *Diabetes Care.* 1996;19(3):252-4.
112. Abbasi F, Chu JW, McLaughlin T, Lamendola C, Leary ET, Reaven GM. Effect of metformin treatment on multiple cardiovascular disease risk factors in patients with type 2 diabetes mellitus. *Metabolism.* 2004 Feb;53(2):159-64.
113. Seufert J, Urquhart R. 2-year effects of pioglitazone add-on to sulfonylurea or metformin on oral glucose tolerance in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2008;79: 453-60.
114. Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Scherthaner G. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. *Diabetes Metab Res Rev.* 2005;21(2):167-74.
115. Charbonnel B, Scherthaner G, Brunetti P, Matthews DR, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia.* 2005;48(6):1093-104. Epub 2005 May 12.
116. Hanefeld M, Brunetti P, Scherthaner GH, Matthews DR, Charbonnel BH; on behalf of the QUARTET Study Group. *Diabetes Care.* 2004 Jan;27(1):141-7.
117. Comaschi M, Corsi A, Di Pietro C, et al. The effect of pioglitazone as add-on therapy to metformin or sulphonylurea compared to a fixed-dose combination of metformin and glibenclamide on diabetic dyslipidaemia. *Nutr Metab Cardiovasc Dis* 2008;18:373-9.
118. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, Komajda M, et al; for the RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes-an interim analysis. *N Engl J Med.* 2007;357(1):28-38.
119. Home P, Pocock S, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;373:2125-35.
120. Home PD, Jones NP, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, et al; for the RECORD Study Group. Rosiglitazone RECORD study: glucose control outcomes at 18 months. *Diabet Med.* 2007;24:626-34.
121. Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. *Am Heart J.* 2013;166(2):240-249.
122. Komajda M, Curtis P, Hanefeld M, et al. Effect of the addition of rosiglitazone to metformin or sulfonylureas versus metformin/sulfonylurea combination therapy on ambulatory blood pressure in people with type 2 diabetes: a randomized controlled trial (the RECORD study). *Cardiovasc Diabetol.* 2008;7:10.
123. Hamann A, Garcia-Puig J, Paul G, et al. Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with type 2 diabetes inadequately controlled on metformin alone. *Exp Clin Endocrinol Diabetes.* 2008 Jan;116(1): 6-13.
124. Duckworth W, Marcelli M, Padden M, et al. Improvements in glycemic control in type 2 diabetes patients switched from sulfonylurea coadministered with metformin to glyburide-metformin tablets. *J Managed Care Pharm.* 2003;9(3):256-62.
125. Blonde L, Wogen J, Kreilick et al. Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide coadministered with metformin. *Diabetes Obes Metab.* 2003;5(6):424-31.
126. Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. *Diabet Med.* 2005 Apr;22:497-502.
127. Swinnen SG, Dain MP, Mauricio D, DeVries JH, Hoeksra JB, Holleman F. Continuation vs discontinuation of insulin secretagogues when initiating insulin in type 2 diabetes. *Diabetes, Obesity and Metabolism.* 2010;12:923-5.
128. Hollander P, Sugimoto D, Vlajnic A, Kilo C. Combination therapy with insulin glargine plus metformin but not insulin glargine plus sulfonylurea provides similar glycemic control to triple oral combination therapy in patients with type 2 diabetes uncontrolled with dual oral agent therapy. *J Diabetes Complications.* 2015 Nov-Dec;29(8):1266-71.

129. Kheirbek RE, Alemi F, Zargoush M. Comparative effectiveness of hypoglycemic medications among veterans. *J Manag Care Pharm.* 2013;19(9):740-44.
130. Mearns ES, Sobieraj DM, White CM, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One.* 2015 Apr 28;10(4):e0125879.
131. Moore LE, Clokey D, Rappaport VJ, et al. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. *Obstet Gynecol* 2010;115:55-9.
132. Mirzamoradi M, Heidar Z, Faalpoor Z, Naeiji Z, Jamali R. Comparison of glyburide and insulin in women with gestational diabetes mellitus and associated perinatal outcome: a randomized clinical trial. *Acta Med Iran.* 2015;53(2):97-103.
133. Poolsup N, Suksomboon N, Amin M (2014) Efficacy and Safety of Oral Antidiabetic Drugs in Comparison to Insulin in Treating Gestational Diabetes Mellitus: A Meta-Analysis. *PLoS ONE* 2014;9(10): e109985. doi:10.1371/journal.pone.0109985.
134. Dezii CM, Kawabata H, Tran M. Effects of once-daily and twice daily dosing on adherence with prescribed glipizide oral therapy for type 2 diabetes. *South Med J.* 2002;95(1):68-71.
135. Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycemic medication in a population of patients with type 2 diabetes: a retrospective cohort study. *Diabet Med.* 2002;19(4):279-84.
136. Melikian C, White TJ, Vanderplas A, et al. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. *Clin Ther.* 2002;24(3):460-7.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Thiazolidinediones
AHFS Class 682028
May 10, 2017**

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β -cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The thiazolidinediones are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹⁻⁴ They are selective agonists of the peroxisome proliferator-activated receptor-gamma (PPAR γ). PPAR receptors are found in tissues important for insulin action. When activated, PPAR γ regulates the transcription of insulin-responsive genes responsible for glucose production, transportation, and utilization. PPAR γ also plays a role in the regulation of fatty acid metabolism. The thiazolidinediones increase the insulin sensitivity of adipose tissue, skeletal muscle, and the liver. This results in increased glucose uptake and metabolism, suppression of hepatic glucose production, and decreased plasma free fatty acid concentrations.¹⁻⁶

Pioglitazone is available in combination with either metformin or glimepiride. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.²⁻⁴ Glimepiride improves glycemic control by stimulating the release of insulin from pancreatic beta cells.²⁻⁴

The thiazolidinediones that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Pioglitazone, pioglitazone-glimepiride, and pioglitazone-metformin are available in generic formulations. Metformin and glimepiride are also available generically in a separate formulation. Pioglitazone is also available in combination with the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin and is included in AHFS class 682005. This class was last reviewed in February 2015.

Table 1. Thiazolidinediones Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Pioglitazone	tablet	N/A	pioglitazone
Rosiglitazone	tablet	Avandia [®]	none
Combination Products			
Pioglitazone and glimepiride	tablet	Duetact ^{®*}	pioglitazone and glimepiride
Pioglitazone and metformin	tablet	Actoplus Met XR [®]	pioglitazone and metformin

*Generic available in at least one dosage form and/or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Thiazolidinediones

Clinical Guideline	Recommendation(s)
<p>American Diabetes Association: Standards of Medical Care in Diabetes (2016)⁷</p>	<p>Current criteria for the diagnosis of diabetes</p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <p>Prevention or delay of type 2 diabetes</p> <ul style="list-style-type: none"> An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially in those with BMI >35 kg/m², those aged <60 years, and women with prior gestational diabetes mellitus. Diabetes self-management education and support programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. <p>Glycemic goals in adults</p> <ul style="list-style-type: none"> Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. <p>Pharmacologic therapy for type 1 diabetes</p> <ul style="list-style-type: none"> Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. Most patients should use of insulin analogs to reduce hypoglycemia risk. Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. <p>Pharmacologic therapy for type 2 diabetes</p> <ul style="list-style-type: none"> At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. If the A_{1c} target is not achieved after approximately three months, consider a

Clinical Guideline	Recommendation(s)
	<p>combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on patient preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia.</p> <ul style="list-style-type: none"> • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. <p><u>Management of diabetes in pregnancy</u></p> <ul style="list-style-type: none"> • <u>Pregestational Diabetes</u> <ul style="list-style-type: none"> ○ Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible, ideally A_{1C} <6.5%, to reduce the risk of congenital anomalies. ○ Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. ○ Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for one year postpartum as indicated by degree of retinopathy. • <u>Gestational Diabetes Mellitus</u> <ul style="list-style-type: none"> ○ Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. ○ Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. • <u>General Principles for Management of Diabetes in Pregnancy</u> <ul style="list-style-type: none"> ○ Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. ○ Fasting, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. • Due to increased red blood cell turnover, A_{1C} is lower in normal pregnancy than in normal nonpregnant women. The A_{1C} target in pregnancy is 6 to 6.5%; <6% may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% if necessary to prevent hypoglycemia.
<p>American Diabetes Association/ European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012 and 2015 Update)^{8,9}</p>	<p><u>Key points</u></p> <ul style="list-style-type: none"> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <p><u>Initial drug therapy</u></p> <ul style="list-style-type: none"> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <p><u>Advancing to dual combination therapy</u></p> <ul style="list-style-type: none"> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability. <p><u>Advancing to triple combination therapy</u></p> <ul style="list-style-type: none"> • Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. • Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the

Clinical Guideline	Recommendation(s)																																																																																						
	<p>degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.</p> <ul style="list-style-type: none"> In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. <p>Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations</p> <table border="1" data-bbox="505 449 1408 1031"> <tr> <td>Initial Drug Monotherapy</td> <td colspan="6">Metformin</td> </tr> <tr> <td>Efficacy (↓HbA_{1c})</td> <td colspan="6">High</td> </tr> <tr> <td>Hypoglycemia</td> <td colspan="6">Low risk</td> </tr> <tr> <td>Weight</td> <td colspan="6">Neutral/loss</td> </tr> <tr> <td>Side Effects</td> <td colspan="6">Gastrointestinal/lactic acidosis</td> </tr> <tr> <td colspan="7">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td> </tr> <tr> <td>Two Drug Combinations</td> <td>Metformin + sulfonyl-urea</td> <td>Metformin + thiazolidinedione (TZD)</td> <td>Metformin + DPP-4 inhibitor</td> <td>Metformin + SGLT2 inhibitor</td> <td>Metformin + GLP-1 receptor agonist</td> <td>Metformin + insulin (usually basal)</td> </tr> <tr> <td>Efficacy (↓HbA_{1c})</td> <td>High</td> <td>High</td> <td>Inter-mediate</td> <td>Inter-mediate</td> <td>High</td> <td>Highest</td> </tr> <tr> <td>Hypoglycemia</td> <td>Moderate risk</td> <td>Low risk</td> <td>Low risk</td> <td>Low risk</td> <td>Low risk</td> <td>High risk</td> </tr> <tr> <td>Weight</td> <td>Gain</td> <td>Gain</td> <td>Neutral</td> <td>Loss</td> <td>Loss</td> <td>Gain</td> </tr> <tr> <td>Major Side Effects</td> <td>Hypoglycemia</td> <td>Edema, heart failure, bone fracture</td> <td>Rare</td> <td>Genito-urinary, dehydration</td> <td>Gastro-intestinal</td> <td>Hypoglycemia</td> </tr> </table> <p>If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</p> <table border="1" data-bbox="505 1079 1408 1451"> <tr> <td>Three Drug Combinations</td> <td>Metformin + sulfonyl-urea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin</td> <td>Metformin + TZD + Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin</td> <td>Metformin + DPP-4 inhibitor + Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin</td> <td>Metformin + SGLT2 inhibitor + Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin</td> <td>Metformin + GLP-1 receptor agonist + Sulfonyl-urea, TZD, or insulin</td> <td>Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist</td> </tr> </table> <p>If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</p> <table border="1" data-bbox="505 1524 1408 1591"> <tr> <td>More Complex Insulin Strategies</td> <td>Combination injectable therapy</td> </tr> </table>	Initial Drug Monotherapy	Metformin						Efficacy (↓HbA _{1c})	High						Hypoglycemia	Low risk						Weight	Neutral/loss						Side Effects	Gastrointestinal/lactic acidosis						If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)							Two Drug Combinations	Metformin + sulfonyl-urea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)	Efficacy (↓HbA _{1c})	High	High	Inter-mediate	Inter-mediate	High	Highest	Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk	Weight	Gain	Gain	Neutral	Loss	Loss	Gain	Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genito-urinary, dehydration	Gastro-intestinal	Hypoglycemia	Three Drug Combinations	Metformin + sulfonyl-urea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + TZD + Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + DPP-4 inhibitor + Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin	Metformin + SGLT2 inhibitor + Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin	Metformin + GLP-1 receptor agonist + Sulfonyl-urea, TZD, or insulin	Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist	More Complex Insulin Strategies	Combination injectable therapy
Initial Drug Monotherapy	Metformin																																																																																						
Efficacy (↓HbA _{1c})	High																																																																																						
Hypoglycemia	Low risk																																																																																						
Weight	Neutral/loss																																																																																						
Side Effects	Gastrointestinal/lactic acidosis																																																																																						
If needed to reach individualized HbA _{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)																																																																																							
Two Drug Combinations	Metformin + sulfonyl-urea	Metformin + thiazolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + SGLT2 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)																																																																																	
Efficacy (↓HbA _{1c})	High	High	Inter-mediate	Inter-mediate	High	Highest																																																																																	
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk																																																																																	
Weight	Gain	Gain	Neutral	Loss	Loss	Gain																																																																																	
Major Side Effects	Hypoglycemia	Edema, heart failure, bone fracture	Rare	Genito-urinary, dehydration	Gastro-intestinal	Hypoglycemia																																																																																	
Three Drug Combinations	Metformin + sulfonyl-urea + TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + TZD + Sulfonyl-urea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or insulin	Metformin + DPP-4 inhibitor + Sulfonyl-urea, TZD, SGLT2 inhibitor, or insulin	Metformin + SGLT2 inhibitor + Sulfonyl-urea, TZD, DPP-4 inhibitor, or insulin	Metformin + GLP-1 receptor agonist + Sulfonyl-urea, TZD, or insulin	Metformin + insulin therapy + TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist																																																																																	
More Complex Insulin Strategies	Combination injectable therapy																																																																																						
<p>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)¹⁰</p>	<ul style="list-style-type: none"> Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. 																																																																																						
<p>American Association of Clinical</p>	<p>Antihyperglycemic pharmacotherapy for type 2 diabetes</p> <ul style="list-style-type: none"> The choice of therapeutic agents should be based on their differing metabolic 																																																																																						

Clinical Guideline	Recommendation(s)
<p>Endocrinologists/ American College Of Endocrinology: Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015)¹¹</p>	<p>actions and adverse effect profiles as described in the 2015 American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm Consensus Statement.</p> <ul style="list-style-type: none"> • Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. • Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. • Thiazolidinediones (TZDs) and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. • When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. • The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. • When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
<p>American Association of Clinical Endocrinologists: Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm 2016 (2016)¹²</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} \leq6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • The therapeutic regimen should be as simple as possible to optimize adherence. <p>Monotherapy</p> <ul style="list-style-type: none"> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ Sodium glucose cotransporter 2 (SGLT-2) inhibitors. ○ DPP-4 inhibitors. ○ . ○ TZDs (use with caution). ○ Alpha-glucosidase inhibitors. • sulfonylureas, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <p>Combination therapy</p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ DPP-4 inhibitors. ○ TZD. ○ Basal insulin. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p>Three-drug combination therapy</p> <ul style="list-style-type: none"> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months have a high likelihood of

Clinical Guideline	Recommendation(s)
	<p>reaching target with a third agent.</p> <ul style="list-style-type: none"> • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfoarea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: <ul style="list-style-type: none"> ○ GLP-1 receptor agonists. ○ SGLT-2 inhibitors. ○ TZD. ○ Basal insulin. ○ DPP-4 inhibitors. ○ Colesevelam. ○ Bromocriptine quick release. ○ Alpha-glucosidase inhibitors. ○ Sulfonylureas and glinides. <p><u>Insulin therapy algorithm</u></p> <ul style="list-style-type: none"> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <p><u>Basal insulin</u></p> <ul style="list-style-type: none"> • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <p><u>Basal-bolus insulin regimens</u></p> <ul style="list-style-type: none"> • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. <p><u>Basal insulin and incretin therapy regimens</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
<p>National Institute for Health and Care Excellence: Type 2 Diabetes in Adults: Management (Published 2015; last updated July 2016)¹³</p>	<p><u>Individualized care</u></p> <ul style="list-style-type: none"> • Adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective. • Take into account any disabilities, including visual impairment, when planning and delivering care for adults with type 2 diabetes. <p><u>HbA_{1c} targets</u></p> <ul style="list-style-type: none"> • Involve adults with type 2 diabetes in decisions about their individual HbA_{1c} target. • For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 6.5%. For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 7.0%. • In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to >7.5%: <ul style="list-style-type: none"> ○ reinforce advice about diet, lifestyle and adherence to drug treatment and ○ support the person to aim for an HbA_{1c} level of 7.0% and ○ intensify drug treatment. • Consider relaxing the target HbA_{1c} level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes: <ul style="list-style-type: none"> ○ who are unlikely to achieve longer-term risk-reduction benefits, for example, people with a reduced life expectancy ○ for whom tight blood glucose control poses a high risk of the consequences of hypoglycemia, for example, people who are at risk of falling, people who have impaired awareness of hypoglycemia, and people who drive or operate machinery as part of their job ○ for whom intensive management would not be appropriate, for example, people with significant comorbidities. • If adults with type 2 diabetes achieve an HbA_{1c} level that is lower than their target and they are not experiencing hypoglycemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA_{1c} level, for example, deteriorating renal function or sudden weight loss. <p><u>Drug treatment</u></p> <ul style="list-style-type: none"> • For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: <ul style="list-style-type: none"> ○ the effectiveness of the drug treatment(s) in terms of metabolic response ○ safety and tolerability of the drug treatment(s) ○ the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy ○ the person's individual preferences and needs ○ the licensed indications or combinations available ○ cost

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. • Initial drug treatment <ul style="list-style-type: none"> ○ Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. ○ Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes. ○ If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. ○ In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m²: <ul style="list-style-type: none"> ▪ Stop metformin if the eGFR is below 30 ml/minute/1.73m². ▪ Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². ○ In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: <ul style="list-style-type: none"> ▪ a dipeptidyl peptidase-4 (DPP-4) inhibitor or ▪ pioglitazone or ▪ a sulfonylurea. ○ In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: <ul style="list-style-type: none"> ▪ heart failure or history of heart failure ▪ hepatic impairment ▪ diabetic ketoacidosis ▪ current, or a history of, bladder cancer ▪ uninvestigated macroscopic hematuria. <p>First intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ metformin and a DPP-4 inhibitor or ○ metformin and pioglitazone or ○ metformin and a sulfonylurea. • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: <ul style="list-style-type: none"> ○ a DPP-4 inhibitor and pioglitazone or ○ a DPP-4 inhibitor and a sulfonylurea or ○ pioglitazone and a sulfonylurea. • Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes. <p>Second intensification of drug treatment</p> <ul style="list-style-type: none"> • In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: <ul style="list-style-type: none"> ○ triple therapy with: metformin, a DPP-4 inhibitor and a sulfonylurea or metformin, pioglitazone and a sulfonylurea or ○ starting insulin-based treatment.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: <ul style="list-style-type: none"> ○ have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or ○ have a BMI lower than 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. • Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 1.0% in HbA_{1c} and a weight loss of at least 3% of initial body weight in six months). • In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with two oral drugs has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider insulin-based treatment. • In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. <p>Insulin-based treatments</p> <ul style="list-style-type: none"> • When starting insulin therapy in adults with type 2 diabetes, use a structured program employing active insulin dose titration that encompasses: <ul style="list-style-type: none"> ○ injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites ○ continuing telephone support ○ self-monitoring ○ dose titration to target levels ○ dietary understanding ○ management of hypoglycemia ○ management of acute changes in plasma glucose control ○ support from an appropriately trained and experienced healthcare professional. • When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. • Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens: <ul style="list-style-type: none"> ○ Offer NPH insulin injected once or twice daily according to need. ○ Consider starting both NPH and short-acting insulin (particularly if the person's HbA_{1c} is 9.0% or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation. ○ Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if: <ul style="list-style-type: none"> ▪ the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or ▪ the person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes or ▪ the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. ○ Consider pre-mixed (biphasic) preparations that include short-acting

Clinical Guideline	Recommendation(s)
	<p>insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if:</p> <ul style="list-style-type: none"> ▪ a person prefers injecting insulin immediately before a meal or ▪ hypoglycemia is a problem or ▪ blood glucose levels rise markedly after meals. <p>○ Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes:</p> <ul style="list-style-type: none"> ▪ who do not reach their target HbA_{1c} because of significant hypoglycemia or ▪ who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached or ▪ who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or ▪ who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. <ul style="list-style-type: none"> • Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). • Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. • Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)¹⁴</p>	<ul style="list-style-type: none"> • Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: <ul style="list-style-type: none"> ○ Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). ○ Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. ○ Inability to comply with standard goals, such as polypharmacy issues. ○ Limited life expectancy or estimated survival of less than 10 years. ○ Cognitive impairment. ○ Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate. <ul style="list-style-type: none"> ○ Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. ○ Metformin can also be used in combination with all other glucose-lowering agents. • Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
<p>International Diabetes Federation Clinical</p>	<p><u>Lifestyle management</u></p> <ul style="list-style-type: none"> • Changing patterns of eating and physical activity can be effective in controlling

Clinical Guideline	Recommendation(s)
<p>Guidelines Task Force: Global Guideline for Type 2 Diabetes (2012)¹⁵</p>	<p>many of the adverse risk factors found in type 2 diabetes.</p> <ul style="list-style-type: none"> • Match the timing of medication (including insulin) and meals. • Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. • Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals. • Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. • Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <p><u>Glucose control levels</u></p> <ul style="list-style-type: none"> • Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. • A lower HbA_{1c} target may be considered if it is easily and safely achieved. • A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <p><u>Oral therapy</u></p> <ul style="list-style-type: none"> • Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. • Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. • First-line therapy <ul style="list-style-type: none"> ○ Begin with metformin unless there is evidence of renal impairment or other contraindication. ○ Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m². ○ Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. ○ In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. • Second-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are not achieved, add a sulfonylurea. ○ Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas. • Third-line therapy <ul style="list-style-type: none"> ○ When glucose control targets are no longer being achieved, start insulin or add a third oral agent. ○ If starting insulin, add basal insulin or use premix insulin. ○ If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD. ○ Another option is to add a glucagon-like peptide-1 (GLP-1) agonist. • Fourth-line therapy <ul style="list-style-type: none"> ○ Begin insulin therapy when optimized oral blood glucose lowering

Clinical Guideline	Recommendation(s)
	<p>mediations (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control.</p> <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
<p>American Academy of Pediatrics: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)¹⁶</p>	<ul style="list-style-type: none"> • Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients <ul style="list-style-type: none"> ○ Who have random venous or plasma blood glucose (BG) concentrations ≥ 250 mg/dL. ○ Whose HbA_{1c} is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: <ul style="list-style-type: none"> ○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' <i>Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines</i> in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
<p>National Institute for Health and Care Excellence: Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Published 2015; last updated November</p>	<p><u>Education and information for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a continuing program of education from diagnosis. Ensure that the programme includes the following core topics: <ul style="list-style-type: none"> ○ insulin therapy, including its aims, how it works, its mode of delivery and dosage adjustment ○ blood glucose monitoring, including targets for blood glucose control (blood glucose and HbA_{1c} levels) ○ the effects of diet, physical activity and intercurrent illness on blood glucose control

Clinical Guideline	Recommendation(s)
<p>2016¹⁷</p>	<ul style="list-style-type: none"> ○ managing intercurrent illness ('sick-day rules', including monitoring of blood ketones [beta-hydroxybutyrate]) ○ detecting and managing hypoglycemia, hyperglykemia and ketosis. • Tailor the education programme to each child or young person with type 1 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul style="list-style-type: none"> ○ personal preferences ○ emotional wellbeing ○ age and maturity ○ cultural considerations ○ existing knowledge ○ current and future social circumstances ○ life goals. • Encourage young people with type 1 diabetes to attend clinic four times a year because regular contact is associated with optimal blood glucose control. • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul style="list-style-type: none"> ○ regular dental examinations ○ an eye examination by an optician every two years. • Encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. • Give children and young people with type 1 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this information after diagnosis and regularly afterwards. • Encourage children and young people with type 1 diabetes to wear or carry something that identifies them as having type 1 diabetes (e.g., a bracelet). • Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) how to find information about government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 1 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. • Children and young people with type 1 diabetes wishing to participate in sports that may have particular risks for people with diabetes should be offered comprehensive advice by their diabetes team. Additional information may be available from local and/or national support groups and organizations, including sports organizations. • Offer education for children and young people with type 1 diabetes and their family members or carers (as appropriate) about the practical issues related to long-distance travel, such as when best to eat and inject insulin when travelling across time zones. <p><u>Insulin therapy for children and young people with type 1 diabetes</u></p> <ul style="list-style-type: none"> • While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen. <ul style="list-style-type: none"> ○ Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. ○ Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. ● Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen. ● Offer children and young people with type 1 diabetes multiple daily injection basal-bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. ● Encourage children and young people with type 1 diabetes who are using multiple daily insulin injection regimens and their family members or carers (as appropriate) to adjust the insulin dose if appropriate after each blood glucose measurement. ● Explain to children and young people with type 1 diabetes using multiple daily insulin injection regimens and their family members or carers (as appropriate) that injecting rapid-acting insulin analogues before eating (rather than after eating) reduces blood glucose levels after meals and helps to optimize blood glucose control. ● Provide all children and young people with type 1 diabetes who are starting continuous subcutaneous insulin infusion (CSII or insulin pump) therapy and their family members or carers (as appropriate) with specific training in its use. Provide ongoing support from a specialist team, particularly in the period immediately after starting continuous subcutaneous insulin infusion. Specialist teams should agree a common core of advice for continuous subcutaneous insulin infusion users. ● Encourage children and young people with type 1 diabetes who are using twice-daily injection regimens and their family members or carers (as appropriate) to adjust the insulin dose according to the general trend in pre-meal, bedtime and occasional night-time blood glucose. ● Explain to children and young people with newly diagnosed type 1 diabetes and their family members or carers (as appropriate) that they may experience a partial remission phase (a 'honeymoon period') during which a low dosage of insulin (0.5 units/kg body weight/day) may be sufficient to maintain an HbA_{1c} level <6.5%. ● Offer children and young people with type 1 diabetes a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences. ● Provide children and young people with type 1 diabetes with insulin injection needles that are of an appropriate length for their body fat. ● Provide children and young people with type 1 diabetes and their family members or carers (as appropriate) with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Offer children and young people with type 1 diabetes a review of injection sites at each clinic visit. ● Provide children and young people with type 1 diabetes with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycemia. ● If a child or young person with type 1 diabetes does not have optimal blood glucose control: <ul style="list-style-type: none"> ○ offer appropriate additional support such as increased contact frequency with their diabetes team, and ○ if necessary, offer an alternative insulin regimen (multiple daily injections, continuous subcutaneous insulin infusion [CSII or insulin

Clinical Guideline	Recommendation(s)
	<p data-bbox="643 205 1341 264">pump] therapy or once-, twice- or three-times daily mixed insulin injections).</p> <p data-bbox="500 296 1211 323"><u>Oral medicines for children and young people with type 1 diabetes</u></p> <ul data-bbox="500 327 1403 541" style="list-style-type: none"> <li data-bbox="500 327 1403 415">• Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain. <li data-bbox="500 420 1403 541">• Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. <p data-bbox="500 573 1373 632"><u>Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes</u></p> <ul data-bbox="500 636 1409 1003" style="list-style-type: none"> <li data-bbox="500 636 1409 724">• Think about the possibility of non-adherence to therapy in children and young people with type 1 diabetes who have suboptimal blood glucose control, especially in adolescence. <li data-bbox="500 728 1409 816">• Be aware that adolescence can be a period of worsening blood glucose control in young people with type 1 diabetes, which may in part be due to non-adherence to therapy. <li data-bbox="500 821 1409 909">• Raise the issue of non-adherence to therapy with children and young people with type 1 diabetes and their family members or carers (as appropriate) in a sensitive manner. <li data-bbox="500 913 1409 1003">• Be aware of the possible negative psychological impact of setting targets that may be difficult for some children and young people with type 1 diabetes to achieve and maintain. <p data-bbox="500 1035 1333 1062"><u>Education and information for children and young people with type 2 diabetes</u></p> <ul data-bbox="500 1066 1419 1919" style="list-style-type: none"> <li data-bbox="500 1066 1419 1314">• Offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. Ensure that the programme includes the following core topics: <ul data-bbox="594 1161 1419 1314" style="list-style-type: none"> <li data-bbox="594 1161 959 1188">○ HbA_{1c} monitoring and targets <li data-bbox="594 1192 1419 1251">○ the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control <li data-bbox="594 1255 1271 1283">○ the aims of metformin therapy and possible adverse effects <li data-bbox="594 1287 1305 1314">○ the complications of type 2 diabetes and how to prevent them. <li data-bbox="500 1318 1419 1619">• Tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: <ul data-bbox="594 1409 1062 1619" style="list-style-type: none"> <li data-bbox="594 1409 862 1436">○ personal preferences <li data-bbox="594 1440 862 1467">○ emotional wellbeing <li data-bbox="594 1472 821 1499">○ age and maturity <li data-bbox="594 1503 886 1530">○ cultural considerations <li data-bbox="594 1535 854 1562">○ existing knowledge <li data-bbox="594 1566 1062 1593">○ current and future social circumstances <li data-bbox="594 1598 748 1625">○ life goals. <li data-bbox="500 1623 1419 1745">• Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) that like others they are advised to have: <ul data-bbox="594 1686 1419 1745" style="list-style-type: none"> <li data-bbox="594 1686 935 1713">○ regular dental examinations <li data-bbox="594 1717 1162 1745">○ an eye examination by an optician every 2 years. <li data-bbox="500 1749 1419 1837">• Encourage children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with their diabetes team. <li data-bbox="500 1841 1419 1919">• Give children and young people with type 2 diabetes and their family members or carers (as appropriate) information about local and/or national diabetes support groups and organizations, and the potential benefits of membership. Give this

Clinical Guideline	Recommendation(s)
	<p>information after diagnosis and regularly afterwards.</p> <ul style="list-style-type: none"> • Explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) how to find information about possible government disability benefits. • Take particular care when communicating with and providing information to children and young people with type 2 diabetes if they and/or their family members or carers (as appropriate) have, for example, physical and sensory disabilities, or difficulties speaking or reading English. <p><u>Dietary management for children and young people with type 2 diabetes</u></p> <ul style="list-style-type: none"> • At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. • Offer children and young people with type 2 diabetes dietetic support to help optimize body weight and blood glucose control. • At each contact with a child or young person with type 2 diabetes, explain to them and their family members or carers (as appropriate) how healthy eating can help to: <ul style="list-style-type: none"> ○ reduce hyperglycemia ○ reduce cardiovascular risk ○ promote weight loss. • Provide dietary advice to children and young people with type 2 diabetes and their family members or carers (as appropriate) in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasize the additional advantages of healthy eating for blood glucose control and avoiding complications. • Take into account social and cultural considerations when providing advice on dietary management to children and young people with type 2 diabetes. • Encourage children and young people with type 2 diabetes to eat at least five portions of fruit and vegetables each day. • At each clinic visit for children and young people with type 2 diabetes: <ul style="list-style-type: none"> ○ measure height and weight and plot on an appropriate growth chart ○ calculate BMI. • Check for normal growth and/or significant changes in weight because these may reflect changes in blood glucose control. • Provide arrangements for weighing children and young people with type 2 diabetes that respect their privacy. <p><u>Metformin</u></p> <ul style="list-style-type: none"> • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
<p>National Institute for Health and Care Excellence: Type 1 diabetes in adults: diagnosis and management (Published 2015; last updated July 2016)¹⁸</p>	<p><u>HbA_{1c} measurement and targets</u></p> <ul style="list-style-type: none"> • Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes. • Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target. • Inform adults with type 1 diabetes of their HbA_{1c} results after each measurement and ensure that their most recent result is available at the time of consultation. • If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal hemoglobin type, estimate trends in blood glucose control using one of the following: <ul style="list-style-type: none"> ○ fructosamine estimation ○ quality-controlled blood glucose profiles ○ total glycated hemoglobin estimation (if abnormal hemoglobins).

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Support adults with type 1 diabetes to aim for a target HbA_{1c} level of < 6.5% to minimize the risk of long-term vascular complications. • Agree an individualized HbA_{1c} target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia. • Ensure that aiming for an HbA_{1c} target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes. <p><u>Self-monitoring of blood glucose</u></p> <ul style="list-style-type: none"> • Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least four times a day, including before each meal and before bed. • Support adults with type 1 diabetes to test at least four times a day, and up to 10 times a day if any of the following apply: <ul style="list-style-type: none"> ○ the desired target for blood glucose control, measured by HbA_{1c} level, is not achieved ○ the frequency of hypoglycemic episodes increases ○ during periods of illness ○ before, during and after sport ○ when planning pregnancy, during pregnancy and while breastfeeding ○ if there is a need to know blood glucose levels more than four times a day for other reasons (for example, impaired awareness of hypoglycemia, high-risk activities). • Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycemia. • Advise adults with type 1 diabetes to aim for: <ul style="list-style-type: none"> ○ a fasting plasma glucose level of 5 to 7 mmol/litre on waking and ○ a plasma glucose level of 4 to 7 mmol/litre before meals at other times of the day. • Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5 to 9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy) • Agree bedtime target plasma glucose levels with each adult with type 1 diabetes that take into account timing of the last meal and its related insulin dose, and are consistent with the recommended fasting level on waking. <p><u>Continuous glucose monitoring</u></p> <ul style="list-style-type: none"> • Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. • Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: <ul style="list-style-type: none"> ○ More than one episode a year of severe hypoglycemia with no obviously preventable precipitating cause. ○ Complete loss of awareness of hypoglycemia. ○ Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities. ○ Extreme fear of hypoglycemia. ○ Hyperglycemia (HbA_{1c} level ≥9%) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA_{1c} can be sustained at or below 7% and/or there has been a fall in HbA_{1c} of 2.5% or more.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. <p><u>Insulin regimens</u></p> <ul style="list-style-type: none"> • Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. • Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only). <p><u>Long-acting insulin</u></p> <ul style="list-style-type: none"> • Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. • Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: <ul style="list-style-type: none"> ○ an existing insulin regimen being used by the person that is achieving their agreed targets ○ once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. • Consider other basal insulin regimens for adults with type 1 diabetes only if the above regimens do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost. <p><u>Rapid-acting insulin</u></p> <ul style="list-style-type: none"> • Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. • Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. • If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. <p><u>Mixed insulin</u></p> <ul style="list-style-type: none"> • Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. • Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. <p><u>Optimizing insulin therapy</u></p> <ul style="list-style-type: none"> • For adults with erratic and unpredictable blood glucose control (hyperglycemia and hypoglycemia at no consistent times), rather than a change in a previously optimized insulin regimen, the following should be considered: <ul style="list-style-type: none"> ○ injection technique ○ injection sites ○ self-monitoring skills ○ knowledge and self-management skills ○ nature of lifestyle ○ psychological and psychosocial difficulties ○ possible organic causes such as gastroparesis. • Give clear guidelines and protocols ('sick-day rules') to all adults with type 1

Clinical Guideline	Recommendation(s)
	<p>diabetes to help them to adjust insulin doses appropriately during periods of illness.</p> <p><u>Adjuncts</u></p> <ul style="list-style-type: none"> Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² (23 kg/m² for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <p><u>Insulin delivery</u></p> <ul style="list-style-type: none"> Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. Provide adults with type 1 diabetes with suitable containers for collecting used needles and other sharps. Arrangements should be available for the suitable disposal of these containers. Check injection site condition at least annually and if new problems with blood glucose control occur.
<p>American Diabetes Association: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)¹⁹</p>	<p><u>Nutritional therapy</u></p> <ul style="list-style-type: none"> Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. <p><u>Physical activity and exercise</u></p> <ul style="list-style-type: none"> Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. Self-monitoring of blood glucose should be performed as frequently as needed,

Clinical Guideline	Recommendation(s)
	<p>and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia.</p> <p><u>Glycemic control goals</u></p> <ul style="list-style-type: none"> • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. <p><u>Insulin therapy</u></p> <ul style="list-style-type: none"> • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. <p><u>Adjunctive therapies</u></p> <ul style="list-style-type: none"> • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the thiazolidinediones are noted in Table 3.

Table 3. FDA-Approved Indications for the Thiazolidinediones¹⁻⁶

Indication	Single Entity Agents		Combination Products	
	Pioglitazone	Rosiglitazone	Pioglitazone and Glimepiride	Pioglitazone and Metformin
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	✓	✓		
Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with both pioglitazone and metformin is appropriate				✓
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes who are already treated with a thiazolidinedione and a sulfonylurea or who have inadequate glycemic control on a thiazolidinedione alone or a sulfonylurea alone			✓	

IV. Pharmacokinetics

The pharmacokinetic parameters of the thiazolidinediones are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Thiazolidinediones⁵

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Pioglitazone	50*	>99	Liver, extensive (% not reported)	Renal (15 to 30)	3 to 7
Rosiglitazone	99	99.8	Liver, extensive (% not reported)	Renal (64), Feces (23)	3 to 4
Combination Products					
Pioglitazone and glimepiride	50*/100	>99	Liver, extensive (% not reported)	Renal (15 to 30)/ Renal (60), Feces (40)	3 to 7/9
Pioglitazone and metformin	50*/50 to 60†	>99/Negligible (% not reported)	Liver, extensive (% not reported)	Renal (15 to 30)/ Renal (90)	3 to 7/ 1.5 to 6.2

*Animal studies.

†Immediate-release.

V. Drug Interactions

Major drug interactions with the thiazolidinediones are listed in Table 5.

Table 5. Major Drug Interactions with the Thiazolidinediones⁵

Generic Name(s)	Interaction	Mechanism
Metformin	Iodine-containing radiopaque agents	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis.
Sulfonylureas	Quinolones	The hypoglycemic effect of sulfonylureas may be increased by quinolones especially in elderly patients with renal compromise. Hypoglycemia symptoms including lightheadedness, diaphoresis, tachycardia and various neurologic and psychiatric disturbances may occur. The mechanism of this interaction is unknown.
Pioglitazone	Tolvaptan	Concurrent use of pioglitazone and tolvaptan may result in decreased tolvaptan plasma concentrations.
Rosiglitazone	Abiraterone	Concurrent use of abiraterone and rosiglitazone may result in increased exposure to rosiglitazone.
Sulfonylureas	Azole antifungals	Azole antifungals may inhibit cytochrome P450 2C9-mediated metabolism of sulfonylureas. The hypoglycemic effects of sulfonylureas may be increased by azole antifungals.

VI. Adverse Drug Events

The most common adverse drug events reported with the thiazolidinediones (TZDs) are listed in Table 6. The boxed warnings for the thiazolidinediones are listed in Tables 7 through 12. The TZDs are associated with a boxed warning regarding the risk of development or exacerbation of congestive heart failure.¹⁻⁴ In November 2013, the FDA announced the removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010. This decision was based on a re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial²⁷ conducted by the Duke Clinical Research Institute²⁹, which determined that recent data for rosiglitazone-containing drugs do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylurea. Under these modifications, distribution of rosiglitazone-containing products is no longer restricted. Health care

professionals, pharmacies, and patients will no longer be required to enroll in the rosiglitazone Risk Evaluation and Mitigation Strategy program to be able to prescribe, dispense, or receive rosiglitazone medicines.²⁰

Table 6. Adverse Drug Events (%) Reported with the Thiazolidinediones¹⁻⁶

Adverse Event	Single Entity Agents		Combination Products	
	Pioglitazone	Rosiglitazone	Pioglitazone and Glimepiride*	Pioglitazone and Metformin*
Cardiovascular				
Anemia	-	-	-	-
Angina	-	✓	-	-
Congestive heart failure	✓	✓	-	-
Myocardial infarction	-	✓	-	-
Myocardial ischemia	-	✓	-	-
Central Nervous System				
Dizziness	-	-	-	4.8 to 5.4
Headache	7 to 9	6	4.0 to 7.1	4.6 to 6.0
Endocrine and Metabolic				
Aggravated diabetes	5	-	-	-
Edema	5 to 15	5 to 15	5.7 to 12.3	2.9 to 11.3
Hyperglycemia	-	4	-	-
Hypoglycemia	✓	✓	13.4 to 15.7	-
Weight gain	✓	✓	9.1 to 13.4	2.9 to 6.7
Gastrointestinal				
Diarrhea	-	2	4.3 to 6.0	4.8 to 5.8
Nausea	-	-	4.0 to 5.1	3.6 to 5.8
Tooth disorder	5	-	-	-
Genitourinary	-	-	-	-
Ovulation	✓	✓	-	-
Hematologic				
Anemia	≤2	2 to 7	-	-
Hematocrit decreased	✓	✓	-	-
Hemoglobin decreased	✓	✓	-	-
Musculoskeletal				
Arthralgia	-	-	-	-
Back pain	-	4	-	-
Fatigue	-	4	-	-
Fracture	5	✓	-	-
Myalgia	3 to 5	-	-	-
Respiratory				
Dyspnea	✓	-	-	-
Pharyngitis	5	-	-	-
Pleural effusion	-	✓	-	-
Pulmonary edema	-	✓	-	-
Sinusitis	6	3	-	4.4 to 5.0
Upper respiratory tract infection	13	10	12.3 to 16.6	12.4 to 15.5
Other				
Cholestatic hepatitis	-	✓	-	-
Hepatotoxicity	Rare	Rare	-	-
Injury	-	8	3.5	-
Macular edema	✓	✓	-	-
Pain in limb	-	-	4.0 to 5.4	-
Urinary tract infection	-	-	5.7 to 6.8	5.3 to 5.8
Viral infection	-	-	-	-

*Adverse reactions for combination therapy only are reported.

-Event not reported.

✓ Percent not specified.

Table 7. Boxed Warning for Actos® (pioglitazone)⁴

WARNING
<p>Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of pioglitazone, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone must be considered. Pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone in patients with established New York Heart Association class III or IV heart failure is contraindicated.</p>

Table 8. Boxed Warning for Duetact® (pioglitazone and glimepiride)²

WARNING
<p>Thiazolidinediones, including pioglitazone, which is a component of Duetact®, cause or exacerbate congestive heart failure in some patients. After initiation of Duetact®, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation of Duetact® must be considered. Duetact® is not recommended in patients with symptomatic heart failure. Initiation of Duetact® in patients with established New York Heart Association Class III or IV heart failure is contraindicated.</p>

Table 9. Boxed Warning for Actoplus Met® (pioglitazone and metformin), Actoplus Met XR® (pioglitazone and metformin extended-release)³

WARNING
<p>Congestive Heart Failure: Thiazolidinediones, including pioglitazone, which is a component of Actoplus Met® and Actoplus Met XR®, cause or exacerbate congestive heart failure in some patients. After initiation of Actoplus Met® or Actoplus Met XR®, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of Actoplus Met® or Actoplus Met XR® must be considered. Actoplus Met® and Actoplus Met XR® are not recommended in patients with symptomatic heart failure. Initiation of Actoplus Met® or Actoplus Met XR® in patients with established New York Heart Association Class III or IV heart failure is contraindicated.</p>
<p>Lactic Acidosis: Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate:pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. If metformin-associated lactic acidosis is suspected, immediately discontinue Actoplus Met® or Actoplus Met XR® and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.</p>

Table 10. Boxed Warning for Avandia® (rosiglitazone)¹

WARNING
<p>Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of rosiglitazone, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of rosiglitazone must be considered. Rosiglitazone is not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone in patients with established NYHA class III or IV heart failure is contraindicated.</p>

VII. Dosing and Administration

The usual dosing regimens for the thiazolidinediones are listed in Table 11.

Table 11. Usual Dosing Regimens for the Thiazolidinediones¹⁻⁶

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Pioglitazone	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes:</u> Tablet: initial, 15 or 30 mg QD; maximum, 45 mg QD	Safety and efficacy in pediatric patients have not been established.	Tablet: 15 mg 30 mg 45 mg
Rosiglitazone	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes:</u> Tablet: initial, 4 mg/day administered as a single dose or in two divided doses; maintenance, 8 mg/day; maximum, 8 mg/day	Safety and efficacy in pediatric patients have not been established.	Tablet: 2 mg 4 mg
Combination Products			
Pioglitazone and glimepiride	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes who are already treated with a thiazolidinedione and a sulfonylurea or who have inadequate glycemic control on a thiazolidinedione alone or a sulfonylurea alone:</u> Tablet: initial, based on patient's current regimen of pioglitazone and/or sulfonylurea, administer QD; maximum, 45-8 mg/day	Safety and efficacy in pediatric patients have not been established.	Tablet: 30-2 mg 30-4 mg
Pioglitazone and metformin	<u>Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with both pioglitazone and metformin is appropriate:</u> Extended-release tablet: initial, based on patient's current regimen of pioglitazone and/or metformin, administer QD; maximum, 45-2,000 mg/day Tablet: initial, based on patient's current regimen of pioglitazone and/or metformin; maximum, 45-2,550 mg/day	Safety and efficacy in pediatric patients have not been established.	Extended-release tablet: 15-1,000 mg 30-1,000 mg Tablet: 15-500 mg 15-850 mg

QD=once daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the thiazolidinediones are summarized in Table 12.

Table 12. Comparative Clinical Trials with the Thiazolidinediones

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Outcomes Trials				
Dormandy et al. ²¹ (2005) PROactive Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.	DB, MC, PC, PRO, RCT Patients 35 to 75 years of age with type 2 diabetes and an HbA _{1c} >6.5% despite treatment with diet alone or with oral glucose-lowering agents with or without insulin and evidence of extensive macrovascular disease as defined by ≥1 of the following: MI or stroke at least 6 months prior to enrollment, percutaneous coronary intervention or coronary artery bypass surgery at least 6 months prior to enrollment, acute coronary syndrome at least 3 months prior to enrollment,	N=5,238 (n=2,605 for pioglitazone; n=2,633 for placebo) 34.5 months (average time of observation)	Primary: Composite of all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle Secondary: Composite of all-cause mortality, nonfatal MI (excluding silent MI) and nonfatal stroke (main secondary end point); cardiovascular death; and time to individual components of the primary composite	Primary: At least one event in the primary composite end point occurred in 514 patients taking pioglitazone and 572 patients taking placebo (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). Secondary: Fewer patients on pioglitazone reached the main secondary end point (composite of all-cause mortality, MI and stroke) compared to patients on placebo (301 vs 358 patients; HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). Significantly more reports of heart failure were noted in patients treated with pioglitazone compared to patients treated with placebo (281 vs 198 patients; P<0.0001). Deaths due to heart failure did not differ significantly between the two study groups (25 for pioglitazone vs 22 for placebo; P=0.634). A greater number of patients on pioglitazone reported edema without heart failure compared to those on placebo (562 vs 341; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>or objective evidence of coronary artery disease or obstructive arterial disease in the leg; patients were excluded if they had type 1 diabetes; were taking insulin only; had planned coronary or peripheral revascularization; had NYHA class II heart failure or above; had ischemic ulcers, gangrene or rest pain in the leg; had had hemodialysis; or had 2.5 times or greater the upper limit of normal concentrations of ALT</p>		end point	
<p>Erdmann et al.²² (2016) Pioglitazone vs placebo Study drugs were taken in addition to</p>	<p>MC, OBS Patients who had previously completed the final visit of PROactive (see above) were eligible for enrolment</p>	<p>N=3,599 Mean 7.8 years</p>	<p>Primary: Composite of all-cause mortality, non-fatal MI (including silent MI), stroke, endovascular or surgical intervention in the coronary or leg arteries, and</p>	<p>Primary: During follow-up (mean 7.8 years), there were no statistically significant differences in the primary or main secondary (death, MI, stroke) endpoints for subjects originally randomized to pioglitazone and placebo, except for leg amputations during follow-up (4.1% pioglitazone, 5.6% placebo; HR, 0.74; 95% CI, 0.55 to 0.99; P=0.046). Secondary: During follow-up, the incidence of total malignancies was similar between groups; bladder cancer was reported in 0.8% of patients (n = 14) in the pioglitazone versus 1.2% (n = 21) in the placebo group (RR, 0.65; 95% CI,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>the patients' glucose-lowering drugs and other medications.</p>			<p>amputation above the ankle</p> <p>Secondary: Composite endpoint comprised non-adjudicated all-cause mortality, non-fatal MI and non-fatal stroke; incidence of malignancies</p>	<p>0.33 to 1.28), and prostate cancer was reported in 44 men (3.7%) in the pioglitazone versus 29 men (2.5%) in the placebo group (RR, 1.47; 95% CI, 0.93 to 2.34).</p>
<p>Wilcox et al.²³ (2007)</p> <p>Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated</p> <p>vs</p> <p>placebo</p> <p>Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.</p>	<p>DB, MC, PC, PRO, RCT</p> <p>Comparison of patients with and without prior stroke enrolled in the PROactive Study (see above)</p>	<p>N=5,238 (n=984 patients with prior stroke; n=4,254 patients without prior stroke)</p> <p>34.5 months (average time of observation)</p>	<p>Primary: Composite of all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle</p> <p>Secondary: Composite of all-cause mortality, nonfatal MI (excluding silent MI) and nonfatal stroke</p>	<p>Primary: In patients with prior stroke (n=486 pioglitazone and n=498 placebo), there was a trend of benefit with pioglitazone compared to placebo for the primary end point of all-cause mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle (event rate, 20.2% pioglitazone vs 25.3% placebo; HR, 0.78; 95% CI, 0.60 to 1.02; P=0.0670).</p> <p>Secondary: In patients with prior stroke, there was a trend of benefit with pioglitazone compared to placebo for the main secondary end point of all-cause mortality, nonfatal MI or nonfatal stroke (event rate, 15.6% with pioglitazone vs 19.7% with placebo; HR, 0.78; 95% CI, 0.58 to 1.06; P=0.1095).</p> <p>In patients with prior stroke, pioglitazone reduced fatal or nonfatal stroke (event rate, 5.6% pioglitazone vs 10.2% placebo; HR, 0.53; 95% CI, 0.34 to 0.85; P=0.0085) and the composite of cardiovascular death, nonfatal MI or nonfatal stroke (event rate, 13.0% with pioglitazone vs 17.7% with placebo; HR, 0.72; 95% CI, 0.52 to 1.00; P=0.0467).</p> <p>Higher event rates were observed in patients with prior stroke compared to those without prior stroke. In patients without prior stroke, no treatment</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>effect was observed for a first stroke.</p> <p>In a subgroup analysis from PROactive, pioglitazone reduced the risk of recurrent stroke significantly in high-risk patients with type 2 diabetes.</p>
<p>Erdmann et al.²⁴ (2007)</p> <p>Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated</p> <p>vs</p> <p>placebo</p> <p>Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.</p>	<p>DB, MC, PC, PRO, RCT</p> <p>Patients who qualified for entry into the PROactive Study on the basis of a previous MI 6 months or more before randomization (see above)</p>	<p>N=2,445 patients with prior MI (n=1,230 in the pioglitazone group; n=1,215 in the placebo group)</p> <p>34.5 months (average time of observation)</p>	<p>Primary: Fatal or nonfatal MI (excluding silent MI); cardiovascular death or nonfatal MI; cardiovascular death, nonfatal MI or stroke; see PROactive Study</p> <p>Secondary: Acute coronary syndrome; composite of nonfatal MI (excluding silent MI), coronary revascularization, acute coronary syndrome, or cardiac death; see PROactive Study</p>	<p>Primary: Pioglitazone significantly reduced the risk of fatal and nonfatal MI (RR, 28%; P=0.045).</p> <p>There were no significant differences in the end point of cardiovascular death or nonfatal MI (P=0.201) or the end point of cardiovascular death, nonfatal MI or stroke (P=0.149).</p> <p>Secondary: Pioglitazone significantly reduced the risk of acute coronary syndrome (RR, 37%; P=0.035).</p> <p>Pioglitazone significantly reduced the risk of the cardiac composite end point of nonfatal MI, coronary revascularization, acute coronary syndrome and cardiac death (RR, 19%; P=0.033).</p> <p>PROactive: The differences in the primary and main secondary end points defined in the main PROactive study did not reach significance in the MI population (P=0.135 and P=0.0585, respectively); however, there was a consistently lower number of events in the pioglitazone-treated patients for all of the end points.</p> <p>The rate of heart failure and heart failure requiring hospitalization (in patients with a previous MI) were significantly higher in the pioglitazone group compared to the placebo group (13.5 vs 9.6%; P=0.003 and 7.5 vs 5.2%; P=0.022, respectively). The rates of fatal heart failure were similar (1.4% with pioglitazone vs 0.9% with placebo; P=0.283).</p>
<p>Erdmann et al.²⁵ (2007)</p> <p>Pioglitazone 15 mg (month 1) QD</p>	<p>DB, MC, PC, PRO, RCT</p> <p>Patients enrolled into the PROactive</p>	<p>N=5,238</p> <p>34.5 months (average time of</p>	<p>Primary: Composite of all-cause mortality, nonfatal MI (including silent</p>	<p>Primary: Among patients with a serious heart failure event, subsequent all-cause mortality was proportionately lower with pioglitazone (40 of 149 [26.8%] vs 37 of 108 [34.3%] with placebo; P=0.1338). Proportionately fewer pioglitazone patients with serious heart failure went on to have an event in</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated</p> <p>vs</p> <p>placebo</p> <p>Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.</p>	<p>study who developed serious heart failure (defined as heart failure that required hospitalization or prolonged a hospitalization stay, was fatal or life threatening, or resulted in persistent significant disability or incapacity) (see above); patients with NYHA Class II-IV heart failure at screening were excluded</p>	<p>observation)</p>	<p>MI), nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle</p> <p>Secondary: Composite of all-cause mortality, nonfatal MI and nonfatal stroke</p>	<p>the primary end point (47.7% with pioglitazone vs 57.4% with placebo; P=0.0593).</p> <p>Secondary: More pioglitazone (5.7%) than placebo patients (4.1%) had a serious heart failure event during the study (P=0.007). However, mortality due to heart failure was similar (25 of 2,605 [0.96%] for pioglitazone vs 22 of 2,633 [0.84%] for placebo; P=0.639).</p> <p>Significantly fewer pioglitazone patients with serious heart failure went on to have an event in the main secondary end point (34.9% with pioglitazone vs 47.2% with placebo; P=0.025).</p>
<p>Wilcox et al.²⁶ (2008)</p> <p>Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated</p> <p>vs</p> <p>placebo</p> <p>Study drugs were taken in addition to the patients'</p>	<p>DB, MC, PC, RCT (PROactive 10 Study)</p> <p>Patients 35 to 75 years of age with type 2 diabetes, HbA_{1c} >6.5% despite treatment with diet or oral antidiabetic agents with or without insulin, and extensive macrovascular disease</p>	<p>N=5,238</p> <p>34.5 months (average time of observation)</p>	<p>Primary: Analysis of the prespecified main secondary end point (MACE) and additional MACE end points (MACE1 through MACE 7) (MACE=all-cause mortality, nonfatal MI, nonfatal stroke; MACE1=cardiovascular mortality, nonfatal MI, or nonfatal stroke; MACE2=all-cause</p>	<p>Primary: Pioglitazone was associated with a 16% reduction in the main secondary end point of MACE compared to placebo (P=0.027).</p> <p>In the pioglitazone group, 9.9% of patients experienced an event from the MACE1 composite end point compared to 11.9% of patients receiving placebo (HR, 0.82; 95% CI, 0.70 to 0.97; P=0.0201).</p> <p>Fewer patients receiving pioglitazone experienced an event from the MACE2 end point compared to placebo (HR, 0.83; 95% CI, 0.72 to 0.96; P=0.0103). A similar result was observed for other end points, including MACE3 (P=0.0051), MACE4 (P=0.0120), MACE5 (P=0.0132), and MACE6 (P=0.0034). There was no significant difference in the MACE7 end point.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glucose-lowering drugs and other medications.			mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome; MACE3=cardiovascular mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome; MACE4=cardiac mortality, nonfatal MI, nonfatal stroke; MACE5=cardiac mortality, nonfatal MI, acute coronary syndrome; MACE6=cardiac mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome; MACE7=cardiac mortality, nonfatal MI Secondary: Not reported	
Home et al. ²⁷ (2007) Rosiglitazone plus either metformin or a sulfonylurea	MC, OL, RCT Patients with type 2 diabetes between 40 and 75 years of age, BMI >25.0 kg/m ² ,	N=4,447 (n=1,117 rosiglitazone plus metformin; n=1,103	Primary: Hospitalization or death from cardiovascular causes	Primary: For adjudicated primary end points (hospitalization or death from cardiovascular causes), the HR was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs metformin plus a sulfonylurea</p>	<p>HbA_{1c} 7.1 to 9.0% while receiving maximum permitted or tolerated doses of metformin or a sulfonylurea; exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension</p>	<p>rosiglitazone plus sulfonylurea; n=2,227 metformin plus sulfonylurea) Mean follow-up 3.75 years for the unplanned interim analyses (study was designed to be 6 years)</p>	<p>Secondary: Death from cardiovascular causes and from any cause, MI, congestive heart failure, and composite of death from cardiovascular causes, MI and stroke</p>	<p>but these events were pending adjudication. Secondary: There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI. Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006).</p>
<p>Home et al.²⁸ (2009) RECORD Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea</p>	<p>MC, OL, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m², on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)</p>	<p>N=4,458 5.5 years (mean follow-up)</p>	<p>Primary: Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and</p>	<p>Primary: The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 patients receiving rosiglitazone and active control, respectively (HR, 0.99; 95% CI, 0.85 to 1.16; P=0.93). Secondary: There was no significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR, 0.84; 95% CI, 0.59 to 1.18; P=0.32), all-cause mortality (HR, 0.86; 95% CI, 0.68 to 1.08; P=0.19), MI (HR, 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR, 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of cardiovascular death, MI, or stroke (HR, 0.93; 95% CI, 0.74 to 1.15; P=0.50).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			stroke	<p>Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR, 2.10; 95% CI, 1.35 to 3.27; P=0.0010).</p> <p>There were no serious adverse event reports of macular edema. The incidence of bone fractures was higher with rosiglitazone compared to active control (RR, 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR, 1.82; 95% CI, 1.37 to 2.41 vs RR, 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on rosiglitazone was primarily in the upper limb (RR, 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR, 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures.</p>
<p>Mahaffey et al.²⁹ (2013) RECORD re-evaluation</p> <p>Rosiglitazone plus either metformin or a sulfonylurea</p> <p>vs</p> <p>metformin plus a sulfonylurea</p>	<p>RETRO</p> <p>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m², on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)</p>	<p>N=4,458</p> <p>5.5 years (mean follow-up)</p>	<p>Primary: Time to first cardiovascular hospitalization or cardiovascular death</p> <p>Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke</p>	<p>Primary: For the primary end point (time to first occurrence of CV (or unknown cause) death, MI, or stroke) no statistically significant difference was observed between rosiglitazone and metformin/sulfonylurea using the original RECORD end point definitions (HR, 0.95; 95% CI, 0.78 to 1.17).</p> <p>For the primary end point, no meaningful difference between rosiglitazone and metformin/sulfonylurea was observed using the original RECORD end point definitions (HR, 0.95; 95% CI 0.78 to 1.17) or new FDA end point definitions (HR, 0.97; 95% CI, 0.79 to 1.18). Furthermore, these results are similar to results from the original RECORD study (HR, 0.93; 95% CI, 0.74 to 1.15).</p> <p>Secondary: The original RECORD study results and the Duke Clinical Research Institute clinical events classification results were also similar for the individual components of the composite end point. These findings and the additional sensitivity analyses performed support the original RECORD results and suggest that when using essentially the same data, the observations were not affected by different clinical events classification processes, physician adjudicators, or end point definitions.</p>
<p>Lincoff et al.³⁰ (2007)</p>	<p>DB, MA, RCT with placebo or active comparator</p>	<p>N=16,390 (19 trials)</p>	<p>Primary: Composite of death from any cause, MI</p>	<p>Primary: Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Pioglitazone monotherapy</p> <p>vs</p> <p>metformin, placebo, sulfonylureas or rosiglitazone</p> <p>or</p> <p>pioglitazone combination therapy with insulin, metformin, or sulfonylureas</p> <p>vs</p> <p>active comparator or placebo</p>	<p>Adult patients with type 2 diabetes and inadequate glycemic control</p>	<p>4 months to 3.5 years</p>	<p>or stroke</p> <p>Secondary: Incidence of serious heart failure</p>	<p>(HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005).</p> <p>Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09).</p> <p>Progressive separation of time-to-event curves became apparent after approximately one year of therapy.</p> <p>Secondary: Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).</p>
<p>Richter et al.³¹ (2006)</p> <p>Pioglitazone monotherapy</p> <p>vs</p> <p>acarbose, metformin, placebo, repaglinide, rosiglitazone, sulfonylurea</p>	<p>MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG</p> <p>Adults with type 2 diabetes, trial duration of at least 24 weeks</p>	<p>22 trials</p> <p>N=6,200 randomized to pioglitazone treatment (total N not reported)</p> <p>24 weeks to 34.5 months</p>	<p>Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects</p> <p>Secondary: Health-related quality of life and HbA_{1c}</p>	<p>Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095).</p> <p>Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>or</p> <p>pioglitazone combination therapy</p> <p>vs</p> <p>combination therapy not containing pioglitazone</p>				<p>hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).</p> <p>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and -0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 kg/m². Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled.</p> <p>Secondary: No study investigated health-related quality of life.</p> <p>Active glucose-lowering compounds like metformin, glibenclamide‡, gliclazide* or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (P values not reported).</p>
<p>Mannucci et al.³² (2008)</p> <p>Pioglitazone</p> <p>vs</p> <p>active comparators, placebo, no treatment</p>	<p>MA (94 trials)</p> <p>Patients treated with pioglitazone (with or without type 2 diabetes)</p>	<p>N=21,180</p> <p>Variable duration</p>	<p>Primary: All-cause mortality, non-fatal coronary event (defined as MI, unstable angina or coronary revascularization), non-fatal chronic heart failure requiring hospitalization</p> <p>Secondary:</p>	<p>Primary: In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality (P value not reported).</p> <p>In non-diabetic patients, only one death was observed occurring among pioglitazone-treated patients.</p> <p>In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR, 0.41; 95% CI, 0.23 to 0.72).</p> <p>When analyzing all trials, no significant reduction of mortality was observed with pioglitazone.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	<p>Comparing different agents, pioglitazone was associated with a lower mortality rate compared to sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars, or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR, 0.22; 95% CI, 0.05 to 1.03), metformin (RR, 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR, 0.49; 95% CI, 0.04 to 5.36), glitazars (RR, 0.42; 95% CI, 0.11 to 1.61), or placebo (RR, 0.16; 95% CI, 0.02 to 1.45).</p> <p>In PROactive, pioglitazone significantly reduced the incidence of non-fatal coronary events (P value not reported).</p> <p>In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported.</p> <p>In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR, 0.82; 95% CI, 0.55 to 1.23).</p> <p>Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant.</p> <p>In PROactive, pioglitazone was associated with an increased risk for chronic heart failure. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR, 1.32; 95% CI, 0.88 to 1.98).</p> <p>Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not significant (P value not reported). When adding PROactive or excluding trials vs dual PPARα/γ agonists pioglitazone was associated with a significant increase of risk for chronic heart failure.</p> <p>In comparison with different agents, pioglitazone was associated with an increased risk of chronic heart failure in PC trials, while differences with sulfonylureas or glitazars did not reach significance.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Nagajothi et al. ³³ (2008) Pioglitazone vs active comparators (metformin and/or sulfonylurea) or placebo	MA (5 trials) Patients treated with pioglitazone	N=not reported Duration varied	Primary: MI Secondary: Stroke, revascularization, total mortality, cardiovascular mortality	Primary: The RR for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17). Secondary: The RR for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07). The RR for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56). The RR for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11). The RR for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47).
Nissen et al. ³⁴ (2007) Rosiglitazone monotherapy or combination therapy vs monotherapy or combination therapy with gliclazide*, glimepiride, glipizide, glyburide, insulin, metformin, placebo	MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and DREAM trials) Mean age of participants was 56 years, mean baseline HbA _{1c} 8.2%	42 trials n=15,560 for rosiglitazone; n=12,283 for comparator 24 to 208 weeks	Primary: MI and death from cardiovascular causes Secondary: Not reported	Primary: Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03). Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06). Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24). Secondary: Not reported
Singh et al. ³⁵ (2007)	MA of RCTs (available up to	4 trials	Primary: RR of MI, heart	Primary: Rosiglitazone significantly increased the risk of MI (94 vs 83; RR, 1.42;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Rosiglitazone vs placebo or other non-TZD oral hypoglycemic agent (including glyburide or metformin)</p>	<p>May 2007 and included ADOPT, DREAM and RECORD trials) of rosiglitazone of at least 12 months duration Study participants with impaired glucose tolerance or type 2 diabetes, studies monitored cardiovascular adverse events and provided numerical data on all adverse events</p>	<p>N=14,291 (n=6,421 rosiglitazone; n=7,870 control) 1 to 4 years</p>	<p>failure, and cardiovascular mortality Secondary: Not reported</p>	<p>95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control. There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53). Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; 95% CI, 0.80 to 1.23; P=0.92). Secondary: Not reported</p>
<p>Richter et al.³⁶ (2007) Rosiglitazone monotherapy vs glyburide, metformin, pioglitazone, placebo, repaglinide or rosiglitazone combination therapy</p>	<p>MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG Adults with type 2 diabetes, trial duration of at least 24 weeks</p>	<p>18 trials N=3,888 randomized to rosiglitazone treatment (total N not reported) 24 weeks to 4 years (median 26 weeks)</p>	<p>Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects Secondary: Health-related quality of life and metabolic control (HbA_{1c})</p>	<p>Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference). The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs combination therapy not containing rosiglitazone</p>				<p>The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in BMI up to 1.5 kg/m². Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01).</p> <p>Secondary: No study investigated health-related quality of life.</p> <p>Active glucose-lowering compounds like metformin, glibenclamide‡ or glimepiride resulted in similar reductions of HbA_{1c} compared to rosiglitazone treatment.</p>
<p>Lago et al.³⁷ (2007) Pioglitazone 15 to 45 mg per day or rosiglitazone 4 to 8 mg per day vs placebo,</p>	<p>MA of DB, RCTs of TZDs that reported risk estimates or frequency data for congestive heart failure and cardiovascular death Patients with prediabetes or type</p>	<p>7 trials N=20,191 29.7 months (range, 12 to 48 months)</p>	<p>Primary: Development of congestive heart failure, risk of cardiovascular death Secondary: Not reported</p>	<p>Primary: Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). The overall event rate for congestive heart failure was 2.3% for patients receiving TZDs and 1.4% in the comparator group.</p> <p>Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of congestive heart failure across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95% CI, 1.21 to 2.42; P=0.002). The risk for congestive heart failure did not</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glibenclamide‡, glimepiride, metformin, metformin plus sulfonyleurea	2 diabetes (with and without cardiovascular disease), mean age 59.2 years, mean BMI 31 kg/m ² , mean baseline HbA _{1c} 7.72%			<p>differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07).</p> <p>The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI, 0.63 to 1.32; P=0.63) or both TZDs (combined RR, 0.93; 95% CI, 0.67 to 1.29; P=0.68). The risk of cardiovascular death did not differ between both drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96).</p> <p>Secondary: Not reported</p>
Karter et al. ³⁸ (2005) Patients initiated pioglitazone (15.2%), sulfonyleureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies	Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001	N=23,440 10.2 months (mean)	<p>Primary: Time-to-incident admission to hospital for congestive heart failure</p> <p>Secondary: Not reported</p>	<p>Primary: Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonyleureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99).</p> <p>Secondary: Not reported</p>
Gerrits et al. ³⁹ (2007) Pioglitazone vs rosiglitazone	RETRO cohort study Patients median age 56 years who were initiated treatment with pioglitazone or rosiglitazone between 2003 and 2006	N=29,911 (n=14,807 pioglitazone; n=15,104 rosiglitazone) 1.2 to 1.3 years	<p>Primary: Risk of hospitalization for acute MI</p> <p>Secondary: Risk of composite of acute MI or coronary revascularization</p>	<p>Primary: Among the patients that initiated pioglitazone, 1.1% of patients were hospitalized for acute MI during follow-up compared to 1.4% for rosiglitazone (no P value reported). The unadjusted HR for hospitalization for acute MI associated with pioglitazone relative to rosiglitazone was 0.82 (95% CI, 0.67 to 1.01; P value not reported). After readjustment for baseline covariants (e.g., medical conditions, procedures and dispensed drugs), the HR was 0.78 (95% CI, 0.63 to 0.96; P value not reported).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>There were 2.6 and 3.1% of patients in the pioglitazone and rosiglitazone groups, respectively, with a first event in the composite end point of acute MI or coronary revascularization. The adjusted HR for the composite of acute MI or coronary revascularization was 0.85 (95% CI, 0.75 to 0.98; P value not reported).</p>
<p>Lipscombe et al.⁴⁰ (2007)</p> <p>Pioglitazone or rosiglitazone</p> <p>vs</p> <p>other oral hypoglycemic agents</p>	<p>Nested case-control analysis of a RETRO cohort study using health care databases in Ontario, Canada</p> <p>Diabetes patients 66 years of age or older treated with at least 1 oral hypoglycemic agent between 2002 and 2005, follow-up until March 31, 2006</p>	<p>N=159,026</p> <p>Median follow-up 3.8 years</p>	<p>Primary: Emergency department visit or hospitalization for congestive heart failure</p> <p>Secondary: Emergency department visit or hospitalization for acute MI, all-cause mortality</p>	<p>Primary: Current treatment with TZD monotherapy was associated with a significantly increased risk of congestive heart failure (78 cases; adjusted RR, 1.60; 95% CI, 1.21 to 2.10; P<0.001) compared to other oral hypoglycemic agent combination therapies (3,478 congestive heart failure cases).</p> <p>The increased risk of congestive heart failure associated with TZD use appeared limited to rosiglitazone.</p> <p>Secondary: Current treatment with TZD monotherapy was associated with a significantly increased risk of acute MI (65 vs 3,695 cases; RR, 1.40; 95% CI, 1.05 to 1.86; P=0.02) and death (102 vs 5,529 cases; RR, 1.29; 95% CI, 1.02 to 1.62; P=0.03) compared to other oral hypoglycemic agent combination therapies.</p>
<p>Saenz et al.⁴¹ (2005)</p> <p>Metformin monotherapy</p> <p>vs</p> <p>placebo, sulfonyleureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic</p>	<p>MA (29 RCTs)</p> <p>Adult patients with type 2 diabetes</p>	<p>N=5,259</p> <p>≥3 months</p>	<p>Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy</p>	<p>Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03).</p> <p>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02).</p> <p>Secondary: Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonyleureas.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
intervention, insulin			requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypoglycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA _{1c} , FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, microalbuminuria, glomerular filtration rate, renal plasma flow	
Type 2 Diabetes – Monotherapy				
Khan et al. ⁴² (2002) Pioglitazone 15 to 45 mg QD vs rosiglitazone 2 to 4 mg QD or 4	OL, PRO, RCT Patients previously stabilized on troglitazone* with stable liver function, baseline HbA _{1c} 7.9% for pioglitazone and 8.0% for	N=186 4 months	Primary: Change in body weight, HbA _{1c} , and lipoproteins Secondary: Not reported	Primary: Both groups experienced equal and significant weight gain of ~2 kg from baseline (P<0.01). No significant change in HbA _{1c} from baseline or difference between groups was observed after four months. Pioglitazone had significant reductions in TC (~ -20 mg/dL†) compared to rosiglitazone (~5 mg/dL†; P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID	rosiglitazone			<p>Pioglitazone had significant reductions in LDL-C (~ -16 mg/dL†) compared to rosiglitazone (~2 mg/dL†; P<0.01).</p> <p>Secondary: Not reported</p>
<p>Goldberg et al.⁴³ (2005)</p> <p>Pioglitazone 30 mg QD, titrated to 45 mg QD after 12 weeks</p> <p>vs</p> <p>rosiglitazone 4 mg QD, titrated to 4 mg BID after 12 weeks</p>	<p>DB, MC, PG, PRO, RCT</p> <p>Patients >35 years of age with type 2 diabetes with HbA_{1c} >7.0%, TG ≥150 mg/dL, LDL-C ≤130 mg/dL and C-peptide ≥1 ng/mL; baseline HbA_{1c} 7.6% for pioglitazone and 7.5% for rosiglitazone; patients were excluded if they had NYHA class III-IV heart failure, MI or stroke in past 6 months; liver disease; serum creatinine >2 mg/dL; receiving renal dialysis or having renal transplant; current glucocorticoid use; receiving any lipid-lowering medication, insulin, combination oral</p>	<p>N=802</p> <p>24 weeks</p>	<p>Primary: Change in TG, lipoproteins, and HbA_{1c}; safety</p> <p>Secondary: Not reported</p>	<p>Primary: TG levels significantly decreased (-51.9 mg/dL) with pioglitazone while TG levels increased with rosiglitazone (13.1 mg/dL; P<0.001).</p> <p>Pioglitazone significantly increased HDL-C (5.2 mg/dL) compared to rosiglitazone (2.4 mg/dL; P<0.001).</p> <p>Non-HDL-C was significantly higher with rosiglitazone (25.7 mg/dL) compared to pioglitazone (3.6 mg/dL; P<0.001).</p> <p>Both treatment groups increased LDL-C, however, smaller increases were observed with pioglitazone (12.3 vs 21.3 mg/dL; P<0.001).</p> <p>LDL particle concentration was reduced with pioglitazone and increased with rosiglitazone (P<0.001). LDL particle size increased more with pioglitazone (P=0.005).</p> <p>Similar reductions in HbA_{1c} were observed with pioglitazone (-0.7%) and rosiglitazone (-0.6%; P=0.129).</p> <p>No difference between agents was observed in adverse events including edema, heart failure, liver function tests, BP, and hypoglycemic episodes.</p> <p>Similar weight gain was observed with pioglitazone (2.0 kg) and rosiglitazone (1.6 kg; P=0.164).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	antidiabetic therapy or weight loss agent; pregnant or breast feeding; receiving therapy for malignancy; or drug or alcohol abuse			
Tran et al. ⁴⁴ (2006) Pioglitazone 45 mg daily vs rosiglitazone 8 mg daily	RETRO Chart review of type 2 diabetic patients who received a TZD for >4 months after inadequate glycemic control on maximally tolerated doses of metformin and a sulfonylurea, baseline HbA _{1c} 9.5% for pioglitazone and 9.3% for rosiglitazone	N=104 1 year	Primary: Proportion of patients with HbA _{1c} ≤7.5% at four and 12 months Secondary: Not specified	Primary: After four months, 62% of patients on pioglitazone (35 total) and 65% of patients on rosiglitazone (31 total) achieved an HbA _{1c} ≤7.5% (P value not reported). Mean HbA _{1c} levels were 7.4% for pioglitazone and 7.5% for rosiglitazone. Of the original population with an HbA _{1c} ≤7.5% at four months, 63% of patients on pioglitazone (22 total) and 61% of patients on rosiglitazone (19 total) maintained an HbA _{1c} ≤7.5% after one year (P value not reported). Secondary: Not specified
Derosa et al. ⁴⁵ (2004) Pioglitazone 15 mg once daily vs rosiglitazone 4 mg once daily	DB, MC, PG, RCT Patients ≥18 years of age with type 2 diabetes and metabolic syndrome, poor glycemic control (HbA _{1c} >7.5%) or experienced adverse effects with diet and oral hypoglycemic agents, such as	N=87 12 months	Primary: Change in baseline BMI, HbA _{1c} , FPG, PPG, fasting plasma insulin, postprandial plasma insulin, HOMA index, lipid profile, and lipoprotein variables; safety Secondary:	Primary: Patients in the pioglitazone and rosiglitazone groups experienced a significant increase in mean BMI at 12 months compared to baseline (4.92 and 6.17%, respectively; both P<0.05). At 12 months, there was a 1.3% improvement from baseline in mean values for HbA _{1c} (P<0.01), 19.3% in FPG (P<0.01), 16.3% in PPG (P<0.01), 42.4% in fasting plasma insulin (P<0.05), and 23.3% in postprandial plasma insulin (P<0.05); no significant differences were found between treatment groups. Significant improvements in mean HOMA index were also observed in both groups compared to baseline (both P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>sulfonylureas or metformin, administered up to maximum tolerated dose</p>		<p>Not reported</p>	<p>Patients receiving pioglitazone experienced a significant improvement at 12 months in almost all variables of lipid metabolism from baseline including TC (-11%), LDL-C (-12%), HDL-C (15%), and Apo B (-10.6%; all P<0.05). Patients receiving rosiglitazone experienced a significant increase in TC (14.9%), LDL-C (16.5%), TG (17.9%), and Apo B (10.3%; all P<0.05).</p> <p>Of the 87 patients who completed the study, three out of 45 patients in the pioglitazone group and five out of 42 patients in the rosiglitazone group had transient, mild-to-moderate adverse events that did not cause withdrawal from the trial.</p> <p>Secondary: Not reported</p>
<p>Derosa et al.⁴⁶ (2006)</p> <p>Pioglitazone 15 mg QD</p> <p>vs</p> <p>rosiglitazone 4 mg QD</p>	<p>DB, MC, PG, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes and metabolic syndrome, poor glycemic control (HbA_{1c} >7.5%) or experienced adverse effects with diet and metformin, administered up to maximum tolerated dose</p>	<p>N=96</p> <p>12 months</p>	<p>Primary: Change in baseline BMI, HbA_{1c}, lipid profile, lipoprotein (a), and homocysteine</p> <p>Secondary: Change in baseline FPG, PPG, and HOMA index</p>	<p>Primary: No BMI change was observed at three, six, nine and 12 months in either group. There was no difference in BMI value between pioglitazone and rosiglitazone (P value not reported).</p> <p>Significant HbA_{1c} decreases were observed at nine (both P<0.05 vs baseline) and 12 months (both P<0.01 vs baseline) in both groups.</p> <p>Significant TC, LDL-C, HDL-C, and TG improvement was present in the pioglitazone group at 12 months compared to the baseline values, and these variations were significantly different than rosiglitazone (P<0.05). No TC, LDL-C, HDL-C, or TG improvement was present in the rosiglitazone group after 12 months.</p> <p>Significant lipoprotein (a) and homocysteine improvement was present in the pioglitazone group at 12 months compared to the baseline values (both P<0.05), and lipoprotein (a) change was significant compared to the rosiglitazone group (P<0.05). A significant homocysteine decrease was observed in the rosiglitazone group at the end of the study (P<0.05).</p> <p>Secondary: After nine and 12 months, mean FPG and PPG levels decreased in both groups compared to baseline (both P<0.05 and P<0.01, respectively).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Berneis et al.⁴⁷ (2008)</p> <p>Pioglitazone 30 mg QD for 4 weeks, then 45 mg QD for 8 weeks</p> <p>vs</p> <p>rosiglitazone 4 mg QD for 4 weeks, then 4 mg BID for 8 weeks</p> <p>All lipid-lowering medications were discontinued 4 weeks prior to the study.</p>	<p>RCT, XO</p> <p>Patients with type 2 diabetes for ≥ 6 months with a stable HbA_{1c} (6.5 to 9.0%) and on a maximum of 2 oral antidiabetic drugs</p>	<p>N=9</p> <p>24 weeks of active treatment (plus an additional 8 week wash-out period)</p>	<p>Primary: Change in HbA_{1c}, insulin sensitivity, lipid parameters</p> <p>Secondary: Not reported</p>	<p>HOMA index improved in both groups at 12 months (P<0.05).</p> <p>Primary: The mean change in HbA_{1c} from baseline to week 12 was -0.54% with pioglitazone and -0.59% with rosiglitazone (P=0.55).</p> <p>Insulin resistance decreased 14% with pioglitazone and 10% with rosiglitazone (P=0.51).</p> <p>There were no significant differences among the treatment groups in the following fasting lipid parameters: HDL-C (P=0.26), LDL-C (P=0.31), LDL size (P=0.51). TC increased more after rosiglitazone compared to pioglitazone (9 vs 3%; P=0.04). TG decreased after treatment with pioglitazone and increased after treatment with rosiglitazone (-21 vs 19%; P=0.004).</p> <p>The only postprandial lipid parameters that demonstrated a significant effect of pioglitazone compared to rosiglitazone was an increased LDL-IIB (5 vs -4%; P=0.001) and a decreased LDL-IIB (-10 vs 10%; P=0.001) after three hours. After six hours, there were no significant changes found.</p> <p>Secondary: Not reported</p>
<p>Chappuis et al.⁴⁸ (2007)</p> <p>Pioglitazone 30 mg QD for 4 weeks, then 45 mg QD for 8 weeks</p> <p>vs</p> <p>rosiglitazone 4 mg QD for 4 weeks, then 4 mg BID for 8 weeks</p>	<p>RCT, XO</p> <p>Patients with type 2 diabetes for ≥ 6 months with a stable HbA_{1c} (6.5 to 9.0%) and on a maximum of 2 oral antidiabetic drugs</p>	<p>N=17</p> <p>24 weeks of active treatment (plus an additional 8 week wash-out period)</p>	<p>Primary: Change in HbA_{1c}, FPG, insulin, insulin sensitivity, non-esterified fatty acids, lipid parameters</p> <p>Secondary: Not reported</p>	<p>Primary: Treatment with pioglitazone and rosiglitazone resulted in similar changes in HbA_{1c} (-0.3 and -0.5%, respectively; P=0.43), FPG (-1.4 and -1.6 mmol/L, respectively; P=0.68), fasting insulin concentrations (-3.9 and -8.2 mU/L, respectively; P=0.33), insulin sensitivity (-2.4 and -4.7 mmol/L \times mU/L, respectively; P=0.33), and fasting non-esterified fatty acids concentrations (0.2 and -0.5 mmol/L; P=0.25).</p> <p>Pioglitazone led to a reduction in fasting TG compared to an increase with rosiglitazone (-0.35 and 0.44 mmol/L, respectively; P=0.037).</p> <p>Pioglitazone did not change the fasting TC concentration, whereas there was an increase with rosiglitazone (0.06 and 0.59 mmol/L, respectively; P=0.031).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>All lipid-lowering medications were discontinued 4 weeks prior to the study.</p>				<p>Pioglitazone did not change the fasting VLDL-protein concentrations within the VLDL fractions, whereas rosiglitazone increased the protein content of VLDL-2 (-2.6 and 17.7 mg/dL, respectively; P=0.035).</p> <p>There were no significant differences on apoB and apoA-I between the groups. Pioglitazone led to a reduction in apoC-II concentrations compared to an increase with rosiglitazone (-0.1 and 1.0 mg/dL, respectively; P=0.022). There was no significant difference in apoC-III (P=0.094) or the apoC-II/apoC-III ratio among the groups.</p> <p>There was no difference in lipoprotein and hepatic lipase activity among patients receiving pioglitazone and rosiglitazone. Cholesterol ester transfer protein activity decreased after treatment with rosiglitazone and increased following treatment with pioglitazone (-6.2 and 4.6 pmol/mL/min, respectively; P<0.001).</p> <p>There was no difference in PPG and post-prandial insulin concentrations between the treatment groups (P=0.944 and P=0.703, respectively). AUC of TG concentrations showed a significant difference between rosiglitazone and pioglitazone (P=0.017). AUC of non-esterified fatty acids concentrations was not significantly different among the treatment groups (P=0.610).</p> <p>The VLDL composition after three and six hours was significantly different following treatment with pioglitazone compared to rosiglitazone, favor of pioglitazone.</p> <p>Secondary: Not reported</p>
<p>Kikuchi et al.⁴⁹ (2012)</p> <p>Pioglitazone 15 to 45 mg/day</p> <p>vs</p>	<p>DB, PG, RCT</p> <p>Drug-naïve Japanese type 2 diabetes patients aged 20 to 75 years with an HbA_{1c}</p>	<p>N=372</p> <p>28 weeks</p>	<p>Primary: Superiority of each active treatment compared to placebo in HbA_{1c} at week 16, and non-inferiority</p>	<p>Primary: Both active treatments were significantly more effective than placebo. The placebo-subtracted HbA_{1c} treatment differences for rosiglitazone and pioglitazone from baseline to week 16 were -0.96% (95% CI, -1.22 to -0.69) and -1.26% (95% CI, -1.56 to -0.97), respectively. In the efficacy evaluable set at week 28, rosiglitazone and pioglitazone had mean changes in HbA_{1c} from baseline of -0.94% and -1.35%, respectively. By the criteria</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone 4 to 8 mg/day vs placebo	≥7.4%		<p>between active agents in HbA_{1c} at week 28, based on a -0.45% margin</p> <p>Secondary: Change in FPG from baseline to week 16, the proportions of HbA_{1c} responders (≥0.7% reduction from baseline in HbA_{1c} or an HbA_{1c} <6.5%) and FPG responders (≥30 mg/dL reduction from baseline in FPG or an FPG <126 mg/dL) at week 28, and changes in fasting HOMA-IR and HOMA-β at week 28</p>	<p>predefined in the study design, non-inferiority of rosiglitazone to pioglitazone was not demonstrated (treatment difference mean -0.41%; 95% CI, -0.64 to -0.18).</p> <p>Secondary: Similar reductions in FPG were seen at week 16 and week 28 with the active agents. The proportion of patients with a ≥0.7% reduction from baseline HbA_{1c} was 56.0% with rosiglitazone and 72.7% with pioglitazone, and the proportion with HbA_{1c} <6.5% was 6.0% and 20.1%, respectively. The proportion of patients with ≥30 mg/dL reduction from baseline FPG was 49.3% with rosiglitazone and 55.4% with pioglitazone and the proportion with FPG <126 mg/dL was 20.0% and 33.1%, respectively. At week 28 in the full analysis set, mean (±SD) HOMA-IR decreased from baseline in both the rosiglitazone (-0.8±4.0) and pioglitazone groups (-1.5±3.7), and HOMA-β increased in both groups (8.6±23.4 and 5.7±19.1, respectively).</p>
Pavo et al. ⁵⁰ (2003) Pioglitazone 30 to 45 mg daily vs metformin 850 to 2,550 mg daily	DB, MC, RCT Recently diagnosed (<12 months) type 2 diabetic patients ≥40 years old, HbA _{1c} 7.5 to 11.0%, and naïve to oral antihyperglycemic medications	N=205 32 weeks	<p>Primary: Change in HbA_{1c} from baseline</p> <p>Secondary: Changes in FPG, fasting serum insulin, and insulin sensitivity</p>	<p>Primary: Each treatment group had a significant reduction in HbA_{1c} from baseline (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.280).</p> <p>Secondary: Each treatment group had a significant reduction in FPG (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.620).</p> <p>Pioglitazone reduced fasting serum insulin significantly (P<0.0001). The change in fasting serum insulin was not significant for metformin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Giles et al.⁵¹ (2008)</p> <p>Pioglitazone 30 to 45 mg QD</p> <p>vs</p> <p>glyburide 10 to 15 mg daily</p> <p>Insulin was the only rescue medication allowed.</p>	<p>DB, MC, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes, HbA_{1c} ≥7.0%, BMI ≤48 kg/m², NYHA functional Class II/III heart failure, left ventricular systolic dysfunction (≤40%), and receiving sulfonylurea therapy (+/- insulin) for ≥30 days before screening or discontinued metformin therapy within 30 days of screening</p>	<p>N=518</p> <p>6 months</p>	<p>Primary: Heart failure progression (defined as the composite of cardiovascular mortality and hospitalization or emergency room visit for heart failure) and metabolic parameters.</p> <p>Secondary: Not reported</p>	<p>(P=0.803). Pioglitazone was significantly more effective than metformin in improving indicators of insulin sensitivity, as determined by reduction of fasting serum insulin (P=0.003) and by analysis of HOMA-S (P=0.002).</p> <p>Primary: Pioglitazone was associated with a higher incidence rate of the composite end point compared with glyburide (13.4 vs 8.2%, respectively; P=0.024).</p> <p>Death from cardiovascular cause was similar between the treatment groups (1.9 and 2.3% for pioglitazone and glyburide, respectively).</p> <p>Overnight hospitalization for heart failure was higher in the pioglitazone group (9.9%) compared to glyburide group (4.7%).</p> <p>Emergency room visits for heart failure occurred in 1.5% of pioglitazone patients compared to 1.2% of glyburide patients.</p> <p>Echocardiographic data demonstrated preserved cardiac function with similar changes in the left ventricular mass index (P=0.959) and left ventricular ejection fraction (P=0.413) among the treatment groups. Cardiac index was significantly increased with pioglitazone compared with glyburide (P=0.012).</p> <p>FPG was significantly decreased with glyburide relative to pioglitazone during the first 4 weeks of treatment. By week 16, a significant difference in mean FPG was observed favoring pioglitazone. At week 24, pioglitazone decreased the HbA_{1c} by -0.98% compared to -0.73% with glyburide (P=0.007).</p> <p>At week 24, significant differences were seen between pioglitazone and glyburide in TGs (-36.8 vs +7.6 mg/dL, respectively; P<0.001), HDL-C (+4.8 vs -0.8 mg/dL, respectively; P<.001), and LDL-C (+6.9 vs -2.4 mg/dL, respectively; P<0.016).</p> <p>Rates of adverse events and serious adverse events were similar between treatment groups. Hypoglycemia was more common with glyburide and edema was more common with pioglitazone. Weight gain was reported as an adverse event more frequently with pioglitazone than glyburide. (6.1 vs</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>2.7%, respectively). Mean weight gain was greater (2.10 vs 1.23 kg, respectively; P=0.012) with pioglitazone than with glyburide.</p> <p>Secondary: Not reported</p>
<p>Kahn et al.⁵² (2006)</p> <p>Rosiglitazone 4 mg QD to 4 mg BID</p> <p>vs</p> <p>glyburide 2.5 mg QD to 7.5 mg BID</p> <p>vs</p> <p>metformin 500 mg QD to 1 g BID</p>	<p>DB, MC, RCT (ADOPT)</p> <p>Patients 30 to 75 years of age recently diagnosed with type 2 diabetes with a FPG 126 to 180 mg/dL</p>	<p>N=4,360</p> <p>4 years</p>	<p>Primary: Time to monotherapy failure (defined as FPG >180 mg/dL after an overnight fast on consecutive testing after at least six weeks of treatment at the maximum-dictated or tolerated dose of study drug)</p> <p>Secondary: Effect on FPG, HbA_{1c}, weight, insulin sensitivity, β-cell function, adverse events</p>	<p>Primary: The cumulative incidence of monotherapy failure at five years was 15% for rosiglitazone, 34% for glyburide and 21% with metformin. This represents a risk reduction of 63% for rosiglitazone as compared with glyburide, and 32% for rosiglitazone as compared with metformin (P<0.001 for both comparisons).</p> <p>Secondary: The rate of progression to a confirmed FPG >140 mg/dL was significantly lower with rosiglitazone than glyburide (RR, 62%; 95% CI, 51 to 72; P<0.001) or metformin (RR, 36%; 95% CI, 15 to 52; P=0.002).</p> <p>At the four-year evaluation, 40% of the patients in the rosiglitazone group had an HbA_{1c} <7.0%, as compared with 26% for glyburide (P<0.001) and 36% for metformin (P=0.03).</p> <p>Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycemia than glyburide (P<0.001 for all comparisons).</p> <p>During the first six months, insulin sensitivity increased more in the rosiglitazone group than in the metformin group. Thereafter, insulin sensitivity improved at similar rates in the two groups, with a significant difference between the two groups noted at four years (P<0.001). Insulin sensitivity did not change significantly in the glyburide group.</p> <p>During the first six months, levels of β-cell function increased more with glyburide than rosiglitazone or metformin. Thereafter, levels of β-cell function declined in all three groups. The annual rate of decline after six months was 6.1% for glyburide (P<0.001), 3.1% for metformin (P=0.02) and 2.0% for rosiglitazone.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>The number of deaths from all causes was similar in the three groups; however, adverse events differed among the groups.</p> <p>Glyburide was associated with a lower risk of cardiovascular events (MI, CHF and stroke) than was rosiglitazone ($P<0.05$), and the risk associated with metformin was similar to that with rosiglitazone. There was no significant difference in the risk for CHF with rosiglitazone compared to metformin (HR, 1.22; 95% CI, 0.66 to 2.26; $P=0.52$), but the risk was significantly higher with rosiglitazone than glyburide (HR, 2.20; 95% CI, 1.01 to 4.79; $P=0.05$).</p> <p>While there was no significant difference noted in men, significantly more women who received rosiglitazone (9.30%) than glyburide (3.47%) or metformin (5.08%) experienced fractures (both $P<0.01$).</p>
<p>Russell-Jones et al.⁵³ (2012) DRUATION-4 Exenatide ER 2 mg SC once weekly vs metformin 2,000 mg/day vs pioglitazone 45 mg/day vs sitagliptin 100</p>	<p>DB, DD, MC, PG, RCT Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m², and stable weight</p>	<p>N=820 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported quality of life</p>	<p>Primary: Decreases in HbA_{1c} were -1.53 ± 0.07, -1.48 ± 0.07, -1.63 ± 0.08, and $-1.15\pm0.08\%$ with exenatide ER, metformin ($P=0.620$ vs exenatide ER), pioglitazone ($P=0.328$ vs exenatide ER), and sitagliptin ($P<0.001$ vs exenatide ER). The HbA_{1c} at trial end was 6.94 ± 0.07, 6.99 ± 0.07, 6.84 ± 0.08, and $7.32\pm0.08\%$ with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively.</p> <p>Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; $P<0.001$), and ≤6.5% compared to patients receiving metformin (49 vs 36%; $P=0.004$) and sitagliptin, respectively (49 vs 26%; $P<0.001$).</p> <p>Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin ($P<0.001$ for both). There were no differences observed with exenatide ER compared to metformin ($P=0.155$ at week 26) and pioglitazone ($P=0.153$ at week 26).</p> <p>Seven-point self-monitored glucose concentrations demonstrated similar</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day				<p>decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments.</p> <p>Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks ($P \leq 0.003$ for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; $P = 0.892$).</p> <p>No clinically significant changes in serum lipids were observed with any treatment.</p> <p>Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin ($P < 0.001$ for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER ($P < 0.001$ for both), and the change with exenatide ER was similar to sitagliptin ($P = 0.329$).</p> <p>Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment.</p> <p>All treatments resulted in improvements in perceived treatment satisfaction, weight-related quality of life, and binge eating behavior. All</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Nichols et al.⁵⁴ (2007)</p> <p>Metformin vs sulfonylurea vs insulin vs TZDs</p>	<p>MC, OS, RETRO</p> <p>Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies</p>	<p>N=9,546</p> <p>≥12 months</p>	<p>Primary: Weight changes</p> <p>Secondary: Not reported</p>	<p>treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported).</p> <p>Primary: Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant.</p> <p>Secondary: Not reported</p>
<p>Norris et al.⁵⁵ (2007)</p> <p>Pioglitazone vs rosiglitazone</p>	<p>MA (112 trials)</p> <p>Patients with metabolic syndrome, pre-diabetes, and type 2 diabetes receiving treatment with pioglitazone or rosiglitazone</p>	<p>N=14,290</p> <p>Duration varied</p>	<p>Primary: HbA_{1c}, lipids, weight, adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: For pioglitazone, the between-group change in HbA_{1c} was -0.99% (95% CI, -1.18 to -0.81) and for rosiglitazone was -0.92% (95% CI, -1.2 to -0.64). Indirect comparison of pioglitazone and rosiglitazone found no significant difference in HbA_{1c} (between-group difference, -0.07%; 95% CI, -0.41 to 0.27).</p> <p>Rosiglitazone increased TC (13.70 mg/dL; 95% CI, 1.06 to 26.35) and pioglitazone decreased TG levels (-1.08 mg/dL; 95% CI, -2.08 to -0.09). Using indirect comparisons, rosiglitazone increased TC compared to pioglitazone (net between-drug effect, 13.91 mg/dL; 95% CI, 1.20 to 26.62).</p> <p>Data were insufficient to assess comparative effects of pioglitazone and rosiglitazone on microvascular and macrovascular events. Few data were available on the comparative effect of pioglitazone and rosiglitazone on cardiovascular risk factors among persons with pre-diabetes or the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>metabolic syndrome. There were insufficient data to determine whether pioglitazone and rosiglitazone have different effects on the incidence of diabetes among persons with either pre-diabetes or the metabolic syndrome.</p> <p>There was limited reporting of adverse events in the available head-to-head trials. Among 719 patients with type 2 diabetes and dyslipidemia, there were no differences between pioglitazone and rosiglitazone at 24-weeks follow-up for weight change (pioglitazone, 2.0 kg and rosiglitazone, 1.6 kg; P=0.164), liver function tests, creatinine phosphokinase, BP, heart rate, hematocrit, hypoglycemic episodes, edema, or congestive heart failure.</p> <p>There were generally no differences in rates of adverse events between the active-treatment and placebo groups. The most frequently reported adverse events were edema, hypoglycemia, and weight gain. Both drugs increased weight compared to placebo: pioglitazone, 2.96 kg (95% CI, 0.73 to 5.20) and rosiglitazone, 2.12 kg (95% CI, 0.89 to 3.36), with no significant difference between the two drugs (95% CI, -1.71 to 3.39).</p> <p>Secondary: Not reported</p>
<p>Singh et al.⁵⁶ (2011)</p> <p>TZDs (pioglitazone, rosiglitazone)</p> <p>vs</p> <p>placebo, sulfonylurea, or metformin</p>	<p>MA, SR (13 RCTs)</p> <p>Type 2 diabetics</p>	<p>N=17,627</p> <p>1 to 5.5 years (follow-up)</p>	<p>Primary: Any pneumonia or lower respiratory tract infection reported as an adverse event, pneumonia or lower respiratory tract infection reported as a serious adverse event</p> <p>Secondary: Not reported</p>	<p>Primary: TZDs are associated with a significantly increased risk for any pneumonia or lower respiratory tract infection compared to control (130/8,163 vs 100/9,464; RR, 1.40; 95% CI, 1.08 to 1.82; P=0.01). In addition TZDs were associated with a significantly increased risk of serious pneumonia or lower respiratory tract infection compared to control (111/7,391 vs 87/8,692; RR, 1.39; 95% CI, 1.05 to 1.83; P=0.02).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Loke et al.⁵⁷ (2009)</p> <p>TZDs (rosiglitazone, pioglitazone, troglitazone*)</p> <p>vs</p> <p>no TZDs</p>	<p>MA (2 OS, 10 RCTs)</p> <p>Type 2 diabetics with impaired glucose</p>	<p>N=45,394</p> <p>≥1 years</p>	<p>Primary: Incidence of fracture, change in baseline BMD</p> <p>Secondary: Not reported</p>	<p>Primary: Rosiglitazone and pioglitazone were associated with a significantly increased risk of fractures overall in the 10 RCTs (OR, 1.45; 95% CI, 1.18 to 1.79; $P<0.001$). Five of these RCTs demonstrated a significantly increased risk of fractures among women (OR, 2.23; 95% CI, 1.65 to 3.01; $P<0.001$), but not among men (OR, 1.00; 95% CI, 0.73 to 1.39; $P=0.98$). The two OS demonstrated an increased risk of fractures with rosiglitazone and pioglitazone.</p> <p>BMD at the lumbar spine (WMD, -1.11%; 95% CI, -2.08 to -0.14; $P=0.02$) and hip (WMD, -1.24%; 95% CI, -2.34 to -0.67; $P<0.001$) significantly decreased in women receiving TZDs within two RCTs. Results from one OS supported these findings (WMD, -1.36%; 95% CI, -2.05 to -0.67; $P=0.001$ and WMD, -1.24%; 95% CI, -1.78 to -0.70; $P<0.001$).</p> <p>Secondary: Not reported</p>
<p>Louisa et al.⁵⁸ (2011)</p> <p>TZDs (pioglitazone, rosiglitazone)</p> <p>vs</p> <p>placebo or other hypoglycemic agents</p>	<p>MA (37 RCTs)</p> <p>Type 2 diabetics</p>	<p>N=3,000</p> <p>>3 months</p>	<p>Primary: Glycemic outcomes</p> <p>Secondary: Change in baseline BMI, lipid profile, BP, high-sensitivity CRP, and insulin sensitizing effect; cardiovascular and clinical endpoints</p>	<p>Primary: Both pioglitazone (WMD, -0.12%; 95% CI, -0.38 to -0.16) and rosiglitazone (WMD, -0.47%; 95% CI, -0.62 to -0.33) significantly decreased HbA_{1c}. Pioglitazone only demonstrated a significant decrease compared to placebo, while rosiglitazone significantly decreased HbA_{1c} compared to placebo and a sulfonylurea.</p> <p>Both pioglitazone (WMD, -9.16 mg/dL; 95% CI, -15.60 to -2.72) and rosiglitazone (WMD, -16.10 mg/dL; 95% CI, -22.20 to -10.01) significantly decreased FPG compared to control. Pioglitazone demonstrated a significant decrease compared to placebo, metformin, and voglibose*, while rosiglitazone significantly decreased FPG compared to placebo, metformin, and a sulfonylurea.</p> <p>Secondary: Pioglitazone and rosiglitazone had similar effects on BMI (pioglitazone: WMD, 0.57; 95% CI, 0.34 to 0.80 and rosiglitazone: WMD, 0.72; 95% CI, 0.29 to 1.14).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Pioglitazone demonstrated a neutral effect of LDL-C (WMD, 3.89 mg/dL; 95% CI, -0.04 to 7.83) and TC (WMD, 2.30 mg/dL; 95% CI, -3.81 to 8.41).</p> <p>Rosiglitazone significantly increased LDL-C (WMD, 11.30 mg/dL; 95% CI, 7.80 to 14.79) and TC (WMD, 7.34 mg/dL; 95% CI, 2.34 to 12.31). Both agents had favorable effects on HDL-C and TGs.</p> <p>Pioglitazone produced a small decrease in DBP and SBP, while rosiglitazone demonstrated a neutral effect.</p> <p>In 13 trials, pioglitazone demonstrated a neutral effect on high sensitivity CRP, while rosiglitazone demonstrated a small improvement in hsCRP.</p> <p>Consistent increase in adiponectin and improvement in HOMA-IR were observed with both pioglitazone and rosiglitazone.</p> <p>Four trials evaluated cardiovascular events as secondary endpoints. There were significant decreases in major cardiac events with both pioglitazone vs control (RR, 0.24; 95% CI, 0.09 to 0.63) and rosiglitazone vs control (RR, 0.41; 95% CI, 0.19 to 0.87).</p>
<p>Xu et al.⁵⁹ (2015) CONFIDENCE</p> <p>Exenatide twice daily vs insulin (75% insulin lispro protamine suspension and 25% insulin lispro injection) twice daily</p>	<p>MC, PG, RCT</p> <p>Treatment-naïve patients, 30 to 70 years of age, with newly diagnosed type 2 diabetes</p>	<p>N=416</p> <p>48 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Effects on weight, blood pressure, lipid profiles and β-cell function</p>	<p>Primary: At week 48, mean HbA_{1c} changes from baseline were -1.8% (95% CI, -1.55 to -2.05%) with exenatide, -1.7% (95% CI, -1.52 to -1.96%) with insulin and -1.5% (95% CI, -1.23 to -1.71%) with pioglitazone. Treatment differences were -0.20% (95% CI, -0.46 to 0.06%) for exenatide vs insulin (P=0.185), and -0.37% (95% CI, -0.63 to -0.12%) for exenatide vs pioglitazone (P=0.002).</p> <p>Secondary: Mean weight change was significantly different between the exenatide group and the insulin and pioglitazone groups from weeks four and eight until the end of the study, with weight decreasing in the exenatide group. Decreases in mean systolic and diastolic blood pressures at 48 weeks were not statistically different between groups, although significant decreases in systolic and diastolic blood pressures were observed with exenatide (P<0.05 vs baseline), and a significant decrease in diastolic blood pressure</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs pioglitazone once daily</p>				<p>alone was found with pioglitazone (P<0.001). Exenatide treatment resulted in improvements in overall lipid profiles, with significant decreases in TG, total cholesterol and LDL cholesterol levels, and an increase in HDL cholesterol (P<0.05 vs baseline for all variables). HDL cholesterol increased with pioglitazone (P<0.001), and LDL cholesterol decreased with insulin (P<0.05).</p> <p>At week 48, HOMA-B (which, together with fasting proinsulin-to-insulin ratio (PI/I), provides an indication of β-cell function during the fasting state) increased in patients treated with insulin (P<0.001 vs baseline). Improvements from baseline were similar in all treatment groups with regard to PI/I, as well as acute insulin response (AIR, which represents β-cell function during the stimulated state after intravenous glucose injection). Disposition index (DI), which provides a measure of β-cell function during the stimulated state under near-physiological conditions of food intake via the gastrointestinal system, increased significantly in all treatment groups (P<0.001 vs baseline for exenatide; P<0.05 vs baseline for insulin and pioglitazone). The greatest mean improvements from baseline in DI and AIR were observed in the exenatide treatment group.</p>
<p>Bolen et al.⁶⁰ (2007) Biguanides vs meglitinides vs TZDs vs α-glucosidase inhibitors</p>	<p>MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs) Patients with type 2 diabetes</p>	<p>N=136 (articles on intermediate outcomes) N=167 (articles on adverse events) N=68 (articles on microvascular outcomes and mortality) Duration varied</p>	<p>Primary: Intermediate outcomes: HbA_{1c}, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes</p> <p>Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart</p>	<p>Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA_{1c} level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.</p> <p>TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C.</p> <p>TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP.</p> <p>Most agents except metformin increased body weight by 1 to 5 kg.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs second-generation sulfonylureas</p>			<p>failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events</p>	<p>In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05).</p> <p>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).</p> <p>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.</p> <p>Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).</p> <p>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.</p> <p>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.</p> <p>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.</p>
<p>Monami et al.⁶¹ (2008) Metformin</p>	<p>MA Patients with type 2 diabetes mellitus</p>	<p>N=7,890 (27 RCT) Variable duration</p>	<p>Primary: Reduction in HbA_{1c} at 16 to 36 months</p>	<p>Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists</p>			<p>Secondary: Not reported</p>	<p>In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.</p> <p>Secondary: Not reported</p>
<p>Shyangdan et al.⁶² (2011)</p> <p>GLP-1 receptor agonist based therapies (albiglutide, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)</p> <p>vs</p> <p>non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)</p>	<p>MA (RCTs)</p> <p>Type 2 diabetics ≥ 18 years of age</p>	<p>N=not reported</p> <p>8 to 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change</p> <p>Secondary: Health-related quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function</p>	<p>Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).</p> <p>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).</p> <p>Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).</p> <p>Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92).</p> <p>Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).</p> <p>Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).</p> <p>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).</p> <p>Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).</p> <p>Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).</p> <p>Secondary: Data on mortality and morbidity were not reported for any treatment.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Quality of life Exenatide ER significantly improved weight-related quality of life and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related quality of life and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.</p> <p>Data for liraglutide were not reported.</p> <p>Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).</p> <p>Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.</p> <p>BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported.</p> <p>FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).</p> <p>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported).</p> <p>PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).</p> <p>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable.</p> <p>Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.</p> <p>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported.</p> <p>β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.</p>
Type 2 Diabetes – Combination Therapy				
<p>Chogtu et al.⁶³ (2009)</p> <p>Pioglitazone (variable doses) and glimepiride 2 mg daily</p> <p>vs</p> <p>rosiglitazone (variable doses) and glimepiride</p>	<p>OL, RCT</p> <p>Patients 30 to 70 years of age with type 2 diabetes who received glimepiride and required a TZD due to a lack of glycemic control, normotensive, and not on antilipemic therapy</p>	<p>N=63</p> <p>12 weeks</p>	<p>Primary: Blood glucose levels, plasma lipids, BP</p> <p>Secondary: Not reported</p>	<p>Primary: The mean change in the FPG and PPG from baseline to week 12 was significant in both groups (P<0.05). There was no significant difference between the groups with regard to the change in FPG (P=0.10) and PPG (P=0.95).</p> <p>HbA_{1c} levels also decreased from baseline to week 12. There was no significant difference between the treatment groups (P>0.05).</p> <p>At week 12, 37.9% of patients in the pioglitazone group and 17.8% of patients in the rosiglitazone group had HbA_{1c} <7.0% (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2 mg daily				<p>TC decreased in both treatment groups; however, to a greater extent with pioglitazone compared to rosiglitazone (P=0.004). TG in the pioglitazone group (P=0.0006) decreased significantly in comparison to the rosiglitazone group (P=0.255) at 12 weeks (P=0.002 pioglitazone vs rosiglitazone). LDL-C decreased significantly (P=0.005) in the pioglitazone group compared to the rosiglitazone group. There was no significant difference in HDL-C among the treatment groups (P>0.05).</p> <p>There was no change in SBP with pioglitazone or rosiglitazone from baseline to week 12. There was also no significant difference in SBP between the treatment groups (P=0.45).</p> <p>There was an increase in the weight following treatment with pioglitazone and rosiglitazone; however, there was no difference between the groups (P=0.10).</p> <p>Secondary: Not reported</p>
<p>Brackenridge et al.⁶⁴ (2009)</p> <p>Pioglitazone 30 mg/day</p> <p>vs</p> <p>rosiglitazone 8 mg/day</p> <p>vs</p> <p>placebo</p> <p>All patients also received metformin.</p>	<p>DB, PC, RCT</p> <p>Type 2 diabetics for ≥6 months currently managed on metformin and diet and exercise</p>	<p>N=24</p> <p>3 months</p>	<p>Primary: Change in baseline lipid profile</p> <p>Secondary: Change in baseline glycemic outcomes</p>	<p>Primary: Of the various lipid concentrations, pioglitazone only significantly decreased non-esterified fatty acid (0.66±0.08 to 0.48±0.04 mmol/L; P=0.02) and VLDL-TG:apoB (31.00±3.91 to 25.30±3.71; P=0.04) compared to baseline. Rosiglitazone also only significantly decreased non-esterified fatty acid (0.68±0.09 to 0.49±0.10; P=0.003) and VLDL-TG:apoB (25.50±2.70 to 20.60±2.47; P=0.01). Placebo significantly increased LDL-C compared to baseline (2.10±0.10 to 2.50±0.19; P=0.03). No significant differences were observed between any of the treatments.</p> <p>Of the various LDL subfraction concentrations, pioglitazone significantly increased LDL3-C compared to placebo (1.25±0.15 to 1.53±0.23 mmol/L; P=0.05). Rosiglitazone significantly increased LDL2-C (1.02±0.14 to 1.39±0.20 mmol/L; P=0.02) and LDL2 apoB (0.25±0.03 to 0.34±0.05 mmol/L; P=0.02), and significantly decreased LDL3-C (1.33±0.12 to 0.96±0.14 mmol/L; P=0.02). Decreases in LDL3-C (P=0.03) and LDL3 apoB (P=0.03) with rosiglitazone were significantly greater compared to pioglitazone.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Of the various lipoprotein metabolism variables, rosiglitazone only decreased VLDL absolute secretion rate compared to baseline (7.24 to 5.83 mg/kg/day; P=0.01). No significant differences were observed between any of the treatments.</p> <p>Secondary: Of the glycemic outcomes evaluated, pioglitazone significantly decreased HbA_{1c} (7.50±0.21 to 6.80±0.18; P=0.01) and significantly increased body weight (96.40±3.62 to 98.30±3.96; P=0.04) and BMI (30.80±1.26 to 31.50±1.45; P=0.04) compared to baseline. Rosiglitazone significantly decreased HbA_{1c} compared to baseline (6.90±0.30 to 6.50±0.19; P=0.04). No significant differences were observed between any of the treatments.</p>
<p>Rosenstock et al.⁶⁵ (2010)</p> <p>Alogliptin 25 mg QD</p> <p>vs</p> <p>alogliptin 12.5 mg QD and pioglitazone 30 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD and pioglitazone 30 mg QD</p> <p>vs</p> <p>pioglitazone 30 mg QD</p>	<p>DB, PG, RCT</p> <p>Treatment naïve patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 11.0%, a BMI 23 to 45 kg/m², who failed diet and exercise interventions for ≥2 months</p>	<p>N=655</p> <p>26 weeks</p>	<p>Primary: Mean change from baseline in HbA_{1c} at week 26</p> <p>Secondary: HbA_{1c} and FPG changes from baseline at each study visit, percentage of patients achieving specific HbA_{1c} goals, frequency of glycemic rescue and safety evaluations</p>	<p>Primary: Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in HbA_{1c} (-1.7 vs -1.0 and -1.2%, respectively; P<0.01 for both comparisons). Similar reductions were observed with the combination therapy arm involving the 12.5 mg strength.</p> <p>Secondary: Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in FPG (-50 vs -26 and -37 mg/dL, respectively; P<0.01 for both comparisons). In addition, each treatment resulted in prompt and progressive reductions in HbA_{1c} and FPG that were sustained throughout the 26 weeks. In addition, both combination therapy groups were associated with significantly greater percentage of patients meeting glycemic goals compared to monotherapy.</p> <p>Fewer patients in the combination therapy groups required hyperglycemic rescue (3.7 and 2.4% with combination alogliptin 12.5 and 25 mg groups, respectively) than with either pioglitazone (6.1%) or alogliptin monotherapy (11.0%).</p> <p>The safety profile of combination therapy was consistent with that of the individual components. The most frequently reported adverse events</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				included headache, back pain, urinary tract infection and peripheral edema.
<p>DeFronzo et al.⁶⁶ (2012)</p> <p>Alogliptin 12.5 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD</p> <p>vs</p> <p>pioglitazone 15 mg QD</p> <p>vs</p> <p>pioglitazone 30 mg QD</p> <p>vs</p> <p>pioglitazone 45 mg QD</p> <p>vs</p> <p>alogliptin 12.5 mg QD and pioglitazone 15 mg QD</p> <p>vs</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.5% to 10.0%, FPG <16.7 mmol/L, BMI 23 to 45 kg/m², blood pressure ≤160/110 mm Hg, HGB ≥12 g/dL (men) or ≥10 g/dL (women), ALT ≤2.5 X ULN, TSH ≤ULN, SCR <133 μmol/L (men) or <124 μmol/L (women), and C-peptide concentration ≥0.26 nmol/L who were inadequately controlled on metformin at a dose of ≥1,500 mg/day for ≥2 months</p>	<p>N=1,554</p> <p>26 weeks</p>	<p>Primary: Mean change from baseline in HbA_{1c} at week 26</p> <p>Secondary: HbA_{1c} and FPG changes from baseline at each study visit, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin/insulin ratio, HOMA-B, achievement of glycemic goals, changes in body weight and safety evaluations</p>	<p>Primary: Coadministration of alogliptin and pioglitazone provided significant improvements in HbA_{1c} and FPG compared to placebo, or either treatment as a single agent added to metformin therapy (P<0.01 for all comparisons).</p> <p>Secondary: More patients in the placebo group (41 of 129; 31.8%) required hyperglycemic rescue than in any active treatment group. The alogliptin and pioglitazone therapy groups had a higher percentage of patients requiring hyperglycemic rescue (8.5 to 14.7%) than any combination therapy (1.5 to 4.6%).</p> <p>Measures of β-cell function found a greater decrease in alogliptin 25 mg/pioglitazone compared to pioglitazone alone. However, the decrease in the alogliptin 12.5 mg/pioglitazone arms were similar to the pioglitazone arms alone.</p> <p>Body weight decreased slightly in patients receiving placebo (-0.7 kg) or alogliptin (-0.02 and -0.7 kg for the 12.5 and 25 mg groups, respectively), whereas there were modest but significant increases in body weight in all groups receiving pioglitazone (P values not reported).</p> <p>In general, the combination of alogliptin and pioglitazone was well tolerated. In addition, the incidence of adverse events was similar across treatment groups.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>alogliptin 12.5 mg QD and pioglitazone 30 mg QD</p> <p>vs</p> <p>alogliptin 12.5 mg QD and pioglitazone 45 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD and pioglitazone 15 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD and pioglitazone 30 mg QD</p> <p>vs</p> <p>alogliptin 25 mg QD and pioglitazone 45 mg QD</p> <p>vs</p> <p>placebo</p>				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients received metformin at a dose of 1,500 mg/day.				
<p>Bosi et al.⁶⁷ (2011)</p> <p>Alogliptin 25 mg QD and pioglitazone 30 mg QD</p> <p>vs</p> <p>pioglitazone 45 mg QD</p> <p>All members received metformin at a dose $\geq 1,500$ mg throughout the study.</p>	<p>AC, DB, MC, PG, RCT</p> <p>Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10%, FPG <15.3 mmol/L, BMI 23 to 45 kg/m², blood pressure $\leq 160/110$ mm Hg, and C-peptide concentration ≥ 0.26 nmol/L who were inadequately controlled on metformin at a dose of $\geq 1,500$ mg/day and pioglitazone 30 mg daily for ≥ 2 months</p>	<p>N=803</p> <p>52 weeks</p>	<p>Primary: Mean change from baseline in HbA_{1c} at weeks 26 and 52</p> <p>Secondary: Mean change from baseline in HbA_{1c} and FPG at all other visits, proportions of patients achieving glycemic goals, proinsulin: insulin ratio, C-peptide, HOMA-B, HOMA insulin resistance, body weight, serum triglycerides, cholesterol, and safety endpoints</p>	<p>Primary: In combination with pioglitazone and metformin, alogliptin was associated with a significantly greater decrease compared to the titration of pioglitazone in HbA_{1c} (-0.7 vs -0.3%, respectively; P=0.025) and FPG (-15 vs -4 mg/L, respectively; P<0.001) at 52 weeks. Similar, the decrease was greater with the alogliptin group at 26 weeks (P<0.001).</p> <p>Secondary: In combination with pioglitazone and metformin, alogliptin was associated with a significantly greater decrease compared to the titration of pioglitazone in FPG (-15 vs -4 mg/L, respectively; P<0.001) at 52 weeks. Decreases favored alogliptin for HbA_{1c} and FPG at 26 weeks and other time points.</p> <p>At week 52, the proportions of patients achieving HbA_{1c} levels ≤ 7.0 (33.2 vs 21.3%, respectively) and $\leq 6.5\%$ (8.7 vs 4.3%, respectively) were significantly higher in the alogliptin group than in the pioglitazone titration group (P<0.001 for all comparisons).</p> <p>Proinsulin: insulin ratio (-0.048 vs -0.007, respectively) and HOMA β-cell function (15.02 vs 2.06, respectively) were significantly improved in the alogliptin group compared to the pioglitazone titration group at 52 weeks (P< 0.001 for all comparisons). However, no statistically significant differences in mean change from baseline in C-peptide, HOMA insulin, in body weight, total cholesterol, HDL cholesterol, LDL-C, triglycerides or free fatty acids resistance were observed between the treatment groups at week 52 (P>0.05 for all comparisons).</p> <p>No meaningful differences in incidences of individual adverse events were observed between treatments.</p>
Einhorn et al. ⁶⁸ (2000)	<p>DB, PC, RCT</p> <p>Patients with poorly</p>	<p>N=328</p> <p>16 weeks</p>	<p>Primary: Change in HbA_{1c}, FPG, insulin,</p>	<p>Primary: Reductions in HbA_{1c} with pioglitazone add-on therapy were significantly lower compared to placebo (-0.83% difference between treatment groups;</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Pioglitazone 30 to 45 mg and metformin (existing therapy)</p> <p>vs</p> <p>metformin (existing therapy)</p>	<p>controlled type 2 diabetes (HbA_{1c} ≥8.0%) with metformin monotherapy</p>		<p>lipoproteins, and C-peptide</p> <p>Secondary: Not reported</p>	<p>P≤0.05).</p> <p>Reductions in FPG with pioglitazone add-on therapy were significantly lower compared to placebo (-37.7 mg/dL difference between treatment groups; P≤0.05).</p> <p>Pioglitazone reduced fasting C-peptide levels (-0.1 ng/mL) while placebo increased levels (0.1 ng/mL; P≤0.05).</p> <p>Pioglitazone reduced fasting C-insulin levels (-2.1 ng/mL) while placebo increased levels (0.4 ng/mL; P<0.05).</p> <p>Pioglitazone add-on therapy significantly reduced TG (-9.7 vs 8.5 mg/dL; P≤0.05) and increased HDL-C (10.2 vs 1.5 mg/dL; P≤0.05) compared to placebo.</p> <p>Both treatment groups increased LDL-C (7.7 vs 11.9 mg/dL; P value not significant).</p> <p>No significant difference between treatment groups in number of adverse events was observed. Higher rate of edema was reported with pioglitazone (5.9 vs 2.5%).</p> <p>Weight loss was observed with placebo (-1.36 kg) while patients receiving pioglitazone had weight gain (0.95 kg; P value not reported).</p> <p>Secondary: Not reported</p>
<p>Kaku et al.⁶⁹ (2009)</p> <p>Pioglitazone 15 to 30 mg QD and metformin 500 to 750 mg daily</p> <p>vs</p>	<p>DB, PC, PG, RCT</p> <p>Patients 20 to 65 years of age with type 2 diabetes, HbA_{1c} 6.5 to 10.0%, who were drug naïve or on metformin</p>	<p>N=169</p> <p>28 weeks</p>	<p>Primary: HbA_{1c}, FPG, fasting insulin, insulin resistance, lipid parameters</p> <p>Secondary: Not reported</p>	<p>Primary: At week 28, mean change in HbA_{1c} from baseline was -0.67% with pioglitazone compared to 0.25% with placebo (P<0.0001).</p> <p>More patients receiving pioglitazone achieved an HbA_{1c} <6.5% compared to placebo (38.6 vs 8.1%, respectively; P<0.0001).</p> <p>At week 28, mean change in FPG from baseline was -20.5 mg/dL with pioglitazone compared to 1.9 mg/dL with placebo (P<0.0001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 500 to 750 mg daily	monotherapy			<p>Mean fasting insulin concentrations were reduced to a greater extent with pioglitazone (-2.15 mU/mL) compared to placebo (-0.38 mU/mL; P=0.021).</p> <p>Insulin resistance was reduced more by pioglitazone compared to placebo (-1.34 vs -0.15; P=0.0025).</p> <p>The main differences in lipids between pioglitazone compared to placebo were significant increases in TC (P=0.0057) and HDL-C (P<0.0001). Adiponectin levels were significantly increased by pioglitazone compared to placebo (P=0.0001).</p> <p>Secondary: Not reported</p>
<p>Perez et al.⁷⁰ (2009)</p> <p>Pioglitazone/ metformin fixed dose combination 15/850 mg BID</p> <p>vs</p> <p>pioglitazone 15 mg BID</p> <p>vs</p> <p>metformin 850 mg BID</p>	<p>DB, PG, RCT</p> <p>Patients ≥18 years of age with type 2 diabetes, HbA_{1c} 7.5 to 10.0%, BMI ≤45 kg/m², who were drug naïve</p>	<p>N=600</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: HbA_{1c} responder rate, changes in baseline FPG, fasting insulin, insulin resistance</p>	<p>Primary: At week 24, mean change in HbA_{1c} from baseline was -1.83% with pioglitazone/metformin compared to -0.96% pioglitazone and -0.99% with metformin (P<0.0001 for combination therapy vs either monotherapy).</p> <p>Secondary: In the pioglitazone/metformin group, 63.8% achieved HbA_{1c} <7.0% compared to 46.9% with pioglitazone and 38.9% with metformin (P value not reported).</p> <p>Pioglitazone/metformin led to the greatest reduction in FPG from baseline to final visit (-39.9 mg/dL) compared to -22.2 mg/dL with pioglitazone and -24.8 mg/dL with metformin (P<0.01 for combination therapy vs either monotherapy).</p> <p>Pioglitazone/metformin led to the greatest reduction in fasting insulin from baseline to final visit (-3.91 μIU/mL), followed by pioglitazone (-3.18 μIU/mL). Both reductions were significantly greater compared to metformin (-0.98 μIU/mL; P<0.05).</p> <p>At week 24, the greatest decrease in insulin resistance was seen with pioglitazone/metformin and pioglitazone compared to metformin;</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				however, the difference was significant only with pioglitazone/metformin (P<0.01).
Kipnes et al. ⁷¹ (2001) Pioglitazone 15 to 30 mg vs placebo All patients received existing sulfonylurea regimens.	DB, MC, PC, RCT Patients on a stable regimen of a sulfonylurea for ≥30 days with an HbA _{1c} ≥8.0%, fasting C-peptide >1 ng/mL, BMI 25 to 45 kg/m ²	N=560 16 weeks	Primary: Change in baseline HbA _{1c} , FPG, TG, and lipoproteins Secondary: Not reported	Primary: Patients receiving pioglitazone and a sulfonylurea had significant decreases (P<0.05) from baseline in HbA _{1c} and FPG levels compared to patients in the placebo and sulfonylurea group. Both pioglitazone and sulfonylurea groups had significant (P<0.05) mean percent decreases in TG levels (-17%; 95% CI, -6 to -27 for 15 mg and -26%; 95% CI, -16 to -36 for 30 mg) and increases in HDL-C levels (6%; 95% CI, 1 to 11 for 15 mg and 13%; 95% CI, 8 to 18 for 30 mg) compared to the placebo and sulfonylurea group. There were small but statistically significant (P≤0.05) mean percent increases in LDL-C levels in all groups. The adverse event rates were similar in all groups. Secondary: Not reported
Matthews et al. ⁷² (2005) Pioglitazone 15 to 45 mg QD and metformin (existing therapy) vs gliclazide* 80 to 320 mg QD and metformin (existing therapy)	DB, RCT Patients with type 2 diabetes that was poorly controlled (HbA _{1c} 7.5 to 11.0%) with metformin monotherapy	N=630 12 months	Primary: Effect on HbA _{1c} Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in HbA _{1c} were observed in pioglitazone- (-0.99%) and gliclazide-treated groups (-1.01%; P=0.837). Secondary: Similar reductions in FPG were observed in pioglitazone- (-2.1 mmol/L) and gliclazide- (-1.6 mmol/L) treated groups (P=0.506). Gliclazide significantly reduced LDL-C compared to pioglitazone (-4.2 vs +10.4 mg/dL; P=0.001). Pioglitazone significantly reduced TG (-53.1 vs -19.5 mg/dL; P<0.001) and increased HDL cholesterol (6.9 mg/dL vs no change; P<0.001) compared to gliclazide.
Charbonnel et al. ⁷³ (2005)	DB, RCT Patients with type 2	N=630 24 months	Primary: Effect on HbA _{1c}	Primary: Similar reductions in HbA _{1c} were observed with pioglitazone add-on therapy (-0.89%) and with gliclazide add-on therapy (-0.77%; P=0.200)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Pioglitazone 15 to 45 mg QD and metformin (existing therapy)</p> <p>vs</p> <p>gliclazide* 80 to 320 mg QD and metformin (existing therapy)</p>	<p>diabetes that was poorly controlled (HbA_{1c} 7.5 to 11.0%) with metformin monotherapy</p>		<p>Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide</p>	<p>after two years.</p> <p>Secondary: Significant reductions in FPG were observed with pioglitazone add-on therapy (–1.8 mmol/L) compared to gliclazide add-on therapy (–1.1 mmol/L; P<0.001) after two years.</p> <p>Gliclazide add-on therapy had significantly reduced LDL-C compared to pioglitazone add-on therapy (–6 vs +2 mg/dL; P<0.001).</p> <p>Pioglitazone add-on therapy significantly reduced TG (–23 vs –7 mg/dL; P<0.001) and increased HDL-C (22 vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy.</p> <p>No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported.</p> <p>Less weight gain was observed with gliclazide add-on therapy to metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg).</p>
<p>Hanefeld et al.⁷⁴ (2004)</p> <p>Pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy)</p> <p>vs</p> <p>metformin 850 to 2,250 mg daily and sulfonylurea (existing therapy)</p>	<p>DB, MC, PG, RCT</p> <p>Patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy</p>	<p>N=639</p> <p>12 months</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: FPG, fasting plasma insulin, lipids, urinary albumin and creatinine (to determine albumin-to-creatinine ratio)</p>	<p>Primary: HbA_{1c} was reduced by 1.20 and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments).</p> <p>Secondary: FPG (P=0.528) and fasting plasma insulin (P=0.199) were also reduced but the between-treatment differences were not statistically significant.</p> <p>Pioglitazone addition to sulfonylurea significantly reduced TG (–16 vs –9%; P=0.008) and increased HDL-C (14 vs 8%; P<0.001) compared with metformin addition.</p> <p>LDL-C was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001).</p> <p>Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone group and increased 2% in the metformin group (P=0.017). Both combinations were well tolerated with no evidence of hepatic or</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Comaschi et al.⁷⁵ (2008)</p> <p>Pioglitazone 15 to 30 mg QD as add-on to existing oral hypoglycemic therapy (either metformin or sulfonylurea)</p> <p>vs</p> <p>metformin/glibenclamide‡ fixed dose combination 400/2.5 mg 1 to 3 tablets daily</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥35 years of age with type 2 diabetes who had received treatment with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months before study entry, HbA_{1c} 7.5 to 11.0%, and fasting C-peptide >0.33 nmol/L</p>	<p>N=250</p> <p>6 months</p>	<p>Primary: Change in HbA_{1c} from baseline to six months</p> <p>Secondary: Change in lipid profiles after six months of treatment</p>	<p>cardiac toxicity in either group.</p> <p>Primary: Pioglitazone-based and fixed-dose metformin/glibenclamide resulted in similar reductions in HbA_{1c} (-1.11 vs -1.29%, respectively; P=0.192) and FPG (-2.13 vs -1.81 mmol/L, respectively; P=0.370).</p> <p>Secondary: No changes in TC were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479).</p> <p>The addition of pioglitazone to metformin or a sulfonylurea led to a slight increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001).</p> <p>There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.01 mmol/L; P=0.677).</p> <p>There was no significant change in LDL-C in patients treated with pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425)</p> <p>There was a significant reduction in TGs with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045).</p>
<p>Seufert et al.⁷⁶ (2008)</p> <p><u>Study 1</u></p> <p>Pioglitazone 15 to 45 mg QD and metformin (existing therapy)</p> <p>vs</p>	<p>2 MC, RCT</p> <p>Patients 35 to 75 years of age with type 2 diabetes who were inadequately controlled on either metformin or sulfonylurea monotherapy (HbA_{1c} 7.5 to</p>	<p>N=1,269</p> <p>104 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline, FPG, glucose excursions using Three hour oral glucose tolerance test, and insulin sensitivity</p> <p>Secondary:</p>	<p>Primary: <u>Study 1</u> The mean change in HbA_{1c} from baseline to week 104 was -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20).</p> <p>The mean change in FPG from baseline to week 104 was -1.8 mmol/l with pioglitazone and metformin compared to -1.1 mmol/l with gliclazide and metformin (P<0.001).</p> <p>Pioglitazone therapy in patients failing metformin therapy achieved</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>gliclazide* 80 to 320 mg daily and metformin (existing therapy)</p> <p><u>Study 2</u> Pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy)</p> <p>vs</p> <p>metformin 850 to 2,550 mg daily and sulfonylurea (existing therapy)</p>	<p>11.0%), and fasting C-peptide >1.5 ng/ml)</p>		<p>Not reported</p>	<p>decreases in glucose excursions at the end of the two-year treatment period. This effect was not seen in the patients receiving gliclazide for two years as add-on therapy to failing metformin.</p> <p>Insulin sensitivity increased when pioglitazone was added to metformin therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001).</p> <p><u>Study 2</u> The mean change in HbA_{1c} from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173).</p> <p>The mean change in FPG from baseline to week 104 was -2.0 mmol/L with pioglitazone and sulfonylurea compared to -1.9 mmol/L with metformin and sulfonylurea (P=0.506).</p> <p>The addition of pioglitazone to failing sulfonylurea therapy for two years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment.</p> <p>Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to sulfonylurea (P=0.581 between treatments).</p> <p>Secondary: Not reported</p>
<p>Home et al.⁷⁷ (2015) HARMONY 5</p> <p>Albiglutide (30 mg/week)</p> <p>vs</p> <p>pioglitazone</p>	<p>DB, MC, PG, RCT</p> <p>Patients ≥18 years of age with a historical diagnosis of type 2 diabetes and inadequate glycaemic control on their current regimen of</p>	<p>N=685</p> <p>156 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to 52 weeks</p> <p>Secondary: HbA_{1c} change over time, FPG, HbA_{1c} responders, body weight change,</p>	<p>Primary: The week 52 model-adjusted difference in change in HbA_{1c} for albiglutide versus placebo was -0.87 (95% CI, -1.07 to -0.68)%-units (P<0.001), and for albiglutide versus pioglitazone it was 0.25 (95% CI, 0.10 to 0.40)%-units; therefore, not non-inferior.</p> <p>Secondary: In the albiglutide group only, fasting plasma glucose reduced rapidly in the first two weeks. Confirmed hypoglycemia occurred in 14% of participants on albiglutide, 25% on pioglitazone and 14% on placebo. The</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(30 mg/day) vs placebo current dose of metformin (>1500 mg/day) was maintained throughout and blinded uptitration of study drug was allowed</p>	<p>metformin and a sulfonylurea</p>		<p>adverse events</p>	<p>mean (\pm standard error) weight change was $-0.42 (\pm 0.2)$ kg with albiglutide, $4.4 (\pm 0.2)$ kg ($P < 0.001$) with pioglitazone, and $-0.40 (\pm 0.4)$ kg with placebo and serious adverse events occurred in 6.3, 9.0 and 6.1% of participants in the respective groups. Injection site reactions occurred in 13% of participants on albiglutide and resulted in treatment discontinuation for four participants (1.4%).</p>
<p>Bergenstal et al.⁷⁸ (2010) DURATION-2 Exenatide ER 2 mg SC once weekly vs sitagliptin 100 mg QD vs pioglitazone 45 mg QD All patients received existing metformin therapy.</p>	<p>DB, DD, MC, PG, RCT Type 2 diabetics ≥ 18 years of age, receiving a stable metformin therapy for ≥ 2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m²</p>	<p>N=514 26 weeks</p>	<p>Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} ≤ 6.5 or $\leq 7.0\%$, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported quality of life, safety</p>	<p>Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c} compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; $P < 0.0001$) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; $P = 0.0165$). Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤ 6.5 ($P < 0.0001$ and $P = 0.0120$) or $\leq 7.0\%$ ($P < 0.0001$ and $P = 0.0015$) compared to patients receiving sitagliptin or pioglitazone. Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; $P = 0.0038$), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; $P = 0.3729$). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤ 7 mmol/L compared to patients receiving sitagliptin (35%; $P < 0.0001$), but no difference was observed between patients receiving pioglitazone (52%; $P = 0.1024$). In all measurements of the six-point self-monitored glucose concentrations</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported).</p> <p>Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001).</p> <p>Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0).</p> <p>Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; P=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; P<0.0001).</p> <p>Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only).</p> <p>All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported).</p> <p>All five domains of weight-related quality of life and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406).</p> <p>The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported.</p>
<p>Aljabri et al.⁷⁹ (2004)</p> <p>Pioglitazone 30 to 45 mg QD</p> <p>vs</p> <p>NPH insulin 0.3 unit/kg QD</p> <p>All patients were receiving existing sulfonylurea or metformin therapy.</p>	<p>OL, RCT</p> <p>Patients with poorly controlled type 2 diabetes (HbA_{1c} >8.0%) with insulin secretagogues and metformin monotherapy</p>	<p>N=62</p> <p>16 weeks</p>	<p>Primary: Effect on HbA_{1c}, FPG, incidence of hypoglycemia (<68 mg/dL), effect on lipoproteins, quality of life (assessed using the DTSQ)</p> <p>Secondary: Not reported</p>	<p>Primary: Similar reductions in HbA_{1c} were observed in pioglitazone-treated (-1.9%) and NPH insulin-treated patients (-2.3%; P=0.32).</p> <p>Nonsignificant differences in reduction in FPG were observed with NPH insulin (-77 mg/dL) and pioglitazone (-52 mg/dL; P=0.07).</p> <p>Significantly more patients reported hypoglycemia with NPH insulin (19) than with pioglitazone (11; P=0.02).</p> <p>Significant increases in HDL-C were observed with pioglitazone (4 mg/dL) compared to NPH insulin (0 mg/dL; P=0.02).</p> <p>No significant differences in TC, LDL-C and TG were reported between the two treatment groups.</p> <p>No significant differences were noted for the DTSQ scores between the two treatment groups.</p> <p>Secondary: Not reported</p>
<p>Dorkhan et al.⁸⁰ (2008)</p> <p>Pioglitazone 30 to 45 mg QD and existing oral hypoglycemic</p>	<p>RCT, OL</p> <p>Patients with type 2 diabetes and inadequate glycemic control (defined as treatment</p>	<p>N=36</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c}, β-cell function, insulin sensitivity, degree of patient satisfaction</p>	<p>Primary: After 26 weeks, the change in HbA_{1c} from baseline was -1.3% (P<0.01) for pioglitazone and -2.2% (P<0.01) for insulin glargine. There was no significant difference between the treatment groups (P=0.050).</p> <p>There was no difference in insulin, β-cell function, or insulin sensitivity among the two treatment groups (P=NS). Insulin glargine resulted in a</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy vs insulin glargine 6 to 10 IU/day administered in the morning (titrated as necessary) and existing oral hypoglycemic therapy	with metformin and sulfonylurea/ meglitinide in doses $\geq 50\%$ of maximum recommended doses and HbA _{1c} >6.2%		Secondary: Not reported	greater reduction in proinsulin concentrations than pioglitazone (-55% vs -25%; P<0.01). Pioglitazone increased HDL-C (0.14 mmol/L) compared to a slight decrease in the insulin glargine group (-0.04 mmol/L; P<0.01 between groups). There were no significant differences between the treatment groups with regards to other lipid parameters (P=NS). The degree of satisfaction with treatment was similar in the pioglitazone and insulin glargine treatment groups. There was a doubling of serum adiponectin levels in the pioglitazone group (7.5 to 15; P<0.01) compared to a significant decrease in the insulin glargine group (8.7 to 7.6; P=0.04; P<0.01 between groups). Secondary: Not reported
Ligvay et al. ⁸¹ (2009) Pioglitazone 15 to 45 mg QD plus glyburide 1.25 mg BID vs insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily All patients were receiving metformin 1,000 mg BID	RCT, OL Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve	N=58 36 months	Primary: HbA _{1c} , rate of treatment failures (defined as HbA _{1c} >8.0%), hypoglycemia, weight gain, compliance, QoL, and patient satisfaction Secondary: Not reported	Primary: After 36 months, HbA _{1c} was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26). The percentage of patients achieving HbA _{1c} <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the HbA _{1c} goal at the end of 36 months. Three patients in each group reached the “treatment failure” end point. The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53). In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) vs 3.36 kg (-0.47 to 7.20; P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doses of medications could be titrated at the investigator's discretion.				<p>Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group.</p> <p>There were differences between the groups for any of the 12 QoL domains evaluated.</p> <p>All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization.</p> <p>Secondary: Not reported</p>
<p>Meneghini et al (abstract).⁸² (2010)</p> <p>Insulin glargine vs pioglitazone</p>	<p>MC, OL, PG</p> <p>Adults with poorly controlled type 2 diabetes (HbA_{1c} 8.0 to 12.0%), despite ≥3 months of sulfonylurea or metformin monotherapy</p>	<p>N=389</p> <p>48 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, BMI, body weight, safety</p>	<p>Primary: At trial end, insulin glargine resulted in a significantly greater reduction in HbA_{1c} compared to pioglitazone (-2.48 vs -1.86%; 95% CI, -0.93 to -0.31; <i>P</i>=0.001).</p> <p>Secondary: Insulin glargine resulted in significantly greater reductions in FPG at all time points (trial end difference, -34.9 mg/dL; 95% CI, -47.6 to -22.2; <i>P</i><0.0001).</p> <p>Changes in weight and BMI were similar between the two treatments.</p> <p>Compared to pioglitazone, insulin glargine resulted in a lower overall incidence of possibly treatment-emergent adverse events (12.0 vs 20.7%) and fewer study discontinuations (2.2 vs 9.1%), but a higher rate (per patient-year) of confirmed clinically relevant hypoglycemic episodes (4.97 vs 1.04; <i>P</i><0.0001) and severe hypoglycemia (0.07 vs 0.01; <i>P</i>=0.0309).</p>
<p>Perez-Monteverde et al.⁸³ (2011)</p> <p>Sitagliptin/metformin vs</p>	<p>DB, RCT</p> <p>Patients with type 2 diabetes and HbA_{1c} 7.5 to 12.0%</p>	<p>N=492 (Phase 1)</p> <p>12 weeks (Phase 1) plus 28 weeks (Phase 2)</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG and two-hour PPG, proportion of patients achieving</p>	<p>Primary: At the end of Phase 1 (12 weeks), mean changes from baseline in HbA_{1c} were -1.0 and -0.9% with sitagliptin and pioglitazone. At the end of Phase 2 (40 weeks), improvements in HbA_{1c} were greater with combination therapy compared to pioglitazone (-1.7 vs -1.4%; <i>P</i>=0.002).</p> <p>Secondary: At the end of Phase 1 (12 weeks), mean changes from baseline were -26.6 and -28.0 mg/dL for FPG and -52.8 and -50.1 mg/dL for two-hour PPG.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>pioglitazone 30 to 45 mg QD</p> <p>In Phase 1, patients were randomized to either sitagliptin 100 mg QD or pioglitazone 30 mg QD. In Phase 2, patients randomized to sitagliptin in Phase 1 were switched to sitagliptin/metformin, and patients randomized to pioglitazone in Phase 1 were up titrated to 45 mg/day</p>			<p>HbA_{1c} <7.0%, safety, body weight</p>	<p>At the end of Phase 2 (40 weeks), improvements in FPG and two-hour PPG were greater with combination therapy compared to pioglitazone (-45.8 vs -37.6 mg/dL; P=0.03 and -90.3 vs -69.1 mg/dL; P=0.001).</p> <p>Significantly more patients receiving combination therapy achieved an HbA_{1c} <7.0% (55.0 vs 40.5%; P=0.004).</p> <p>A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of edema were observed with combination therapy compared to pioglitazone. The incidence of hypoglycemia was similarly low with both treatments.</p> <p>Body weight decreased with combination therapy and increased with pioglitazone (-1.1 vs 3.4 kg; P<0.001).</p>
<p>Wainstein et al.⁸⁴ (2012)</p> <p>Sitagliptin/metformin 50/500 mg BID, titrated up to 50/1,000 mg BID</p> <p>vs</p> <p>pioglitazone 30 mg/day, titrated up to 45 mg/day</p>	<p>DB, RCT</p> <p>Treatment-naïve patients with type 2 diabetes HbA_{1c} 7.5 to 12.0%</p>	<p>N=517</p> <p>32 weeks</p>	<p>Primary: Change from baseline HbA_{1c}, proportion of patients who achieved HbA_{1c} <7.0%</p> <p>Secondary: Change from baseline FPG</p>	<p>Primary: The least squares mean changes in HbA_{1c} at week 32 were -1.9 and -1.4% with combination therapy compared to pioglitazone, respectively (between-group differences, -0.5%; P<0.001).</p> <p>A greater proportion of patients achieved an HbA_{1c} <7.0% at week 32 with combination therapy compared to pioglitazone (57 vs 43%; P<0.001).</p> <p>Secondary: Compared to pioglitazone, combination therapy resulted in a greater least squares mean reductions in FPG (-56.0 vs -44.0 mg/dL; P<0.001) and 2-hour PPG (-102.2 vs -82.0 mg/dL; P<0.001) at week 32. A substantially greater reduction in FPG (-40.5 vs -13.0 mg/dL; P<0.001) was observed at week 1 with combination therapy compared to pioglitazone.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>A greater reduction in the fasting proinsulin:insulin and a greater increase in HOMA-B were observed with combination therapy compared to pioglitazone, while greater decreases in fasting insulin and HOMA-IR, and a greater increase in quantitative insulin sensitivity check index were observed with pioglitazone compared to combination therapy.</p> <p>Combination therapy resulted in a decrease in body weight (-1.4 kg) and pioglitazone resulted in an increase in body weight (3.0 kg; P<0.001).</p> <p>Higher incidences of diarrhea (15.3 vs 4.3%; P<0.001), nausea (4.6 vs 1.2%; P=0.02), and vomiting (1.9 vs 0.0%; P=0.026), and a lower incidence of edema (1.1 vs 7.0%; P<0.001) were observed with combination therapy compared to pioglitazone.</p> <p>There was no difference between the two treatments in the incidence of hypoglycemia (8.4 vs 8.3%; P=0.055).</p>
<p>Takahata et al.⁸⁵ (2013)</p> <p>Sitagliptin 50 mg/day</p> <p>vs</p> <p>pioglitazone 15 mg/day</p> <p>(both groups could have doses titrated up at 16 weeks if HbA_{1c} ≥6.5%)</p>	<p>MC, OL, RCT</p> <p>Japanese type 2 diabetic men and women between the ages of 20 and 75 years whose diabetes had been inadequately controlled (HbA_{1c}, 6.9 to 9.5%) with metformin and/or sulfonylurea.</p>	<p>N=130</p> <p>Up to 24 weeks</p>	<p>Primary: Difference in the mean changes in the HbA_{1c} level from baseline at 24 weeks</p> <p>Secondary: Levels of FPG, fasting insulin, inflammation mediators, N-terminal pro-B-type natriuretic peptide, and markers of lipids, uric acid, liver function, and renal function</p>	<p>Primary: Difference in HbA_{1c} in the sitagliptin group was -0.86 and in the pioglitazone group was -0.58 (P=0.024).</p> <p>Secondary: Difference in FPG and fasting insulin did not differ significantly between groups. Body weight decreased by 0.29 kg in the sitagliptin group and increased by 1.70 kg in the pioglitazone group (P<0.001). The levels of LDL-C and HDL-C were significantly decreased in the sitagliptin group. The triglyceride level was not altered. The Estimated glomerular filtration rate and creatinine level were significantly exacerbated in both groups, and the uric acid level was also exacerbated in the sitagliptin group.</p> <p>Hypoglycemia (3.4 vs 3.5%), gastrointestinal symptoms (5.2 vs 1.8%) and pedal edema (0 vs 68.4%, P<0.001) were observed for 24 weeks in the sitagliptin and pioglitazone groups, respectively. No severe cases of hypoglycemia, rash, or bone fracture were observed in either group during the trial.</p>
<p>Borges et al.⁸⁶ (2011)</p>	<p>DB, MC, RCT</p>	<p>N=688</p>	<p>Primary: Change in baseline</p>	<p>Primary: Combination therapy was more efficacious in achieving significant</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Rosiglitazone/ metformin</p> <p>vs</p> <p>metformin</p>	<p>Drug naïve patients with type 2 diabetes</p>	<p>18 months</p>	<p>HbA_{1c}, FPG</p> <p>Secondary: Bone mineral density</p>	<p>reductions in HbA_{1c} (P<0.0001) and FPG (P<0.001) compared to metformin. In addition, more patients achieved HbA_{1c} and FPG goals with combination therapy compared to metformin.</p> <p>Secondary: In a bone substudy, at week 80 combination therapy was associated with significantly lower BMD compared to metformin in the lumbar spine (P<0.0012) and total hip (P=0.0005, respectively). There was no difference between treatments for distal one-third of radius, femoral neck, and total bone mineral densities (P values not reported).</p>
<p>Fonseca et al.⁸⁷ (2000)</p> <p>Rosiglitazone 4 mg and metformin 2,500 mg daily</p> <p>vs</p> <p>rosiglitazone 8 mg and metformin 2,500 mg daily</p> <p>vs</p> <p>metformin 2,500 mg daily</p>	<p>DB, PC, RCT</p> <p>Patients with poorly controlled type 2 diabetes (mean FPG 140 to 300 mg/dL) with metformin; baseline HbA_{1c} 8.6% in the metformin treatment group, 8.9% in the rosiglitazone/metformin 4/2,500 mg treatment group and 8.9% in the rosiglitazone/metformin 8/2,500 mg treatment group; patients were excluded if they had NYHA class III-IV heart failure, angina, renal or liver disease, symptomatic neuropathy, or prior use of rosiglitazone</p>	<p>N=348</p> <p>26 weeks</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, fructosamine, C-peptide, FFA, lipids, lactate, and estimates of insulin sensitivity (HOMA-S) and β-cell function (HOMA-B)</p> <p>Secondary: Not reported</p>	<p>Primary: Addition of rosiglitazone significantly reduced HbA_{1c} in a dose-related fashion from baseline compared to metformin monotherapy. Mean difference from the metformin control group was -1.0% (P<0.001) with rosiglitazone/metformin 4/2,500 mg and -1.2% with rosiglitazone/metformin 8/2,500 mg (P<0.001).</p> <p>Mean FPG concentrations were reduced significantly with rosiglitazone/metformin 4/2,500 mg (-33 mg/dL; P<0.0001) and with rosiglitazone/metformin 8/2,500 mg (-48.4 mg/dL; P<0.0001). No significant change in FPG was observed with metformin monotherapy.</p> <p>Fructosamine levels were reduced with both rosiglitazone/metformin 4/2,500 mg (-27.9 μmol/L; P value not reported) and rosiglitazone/metformin 8/2,500 mg (-36.8 μmol/L; P value not reported). Fructosamine levels increased with metformin monotherapy (12.3 μmol/L; P value not reported).</p> <p>C-peptide values were reduced significantly in all treatment groups compared to baseline (P<0.05).</p> <p>FFA levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05).</p> <p>Significant increases in TC, HDL-C and LDL-C were observed with both rosiglitazone groups when compared to metformin monotherapy group (P<0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	or insulin			<p>Mean fasting lactate levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05).</p> <p>Both insulin sensitivity (as measured by HOMA-S) and β-cell function (as measured by HOMA-B) were increased in a dose-dependent fashion with rosiglitazone/metformin compared to metformin monotherapy (P value not reported).</p> <p>Secondary: Not reported</p>
<p>Weissman et al.⁸⁸ (2005)</p> <p>Rosiglitazone 8 mg QD and metformin 1,000 mg/day (RSG + MET)</p> <p>vs</p> <p>metformin 1,500 mg/day (MET)</p>	<p>DB, MC, PG, RCT</p> <p>Patients 18 to 75 years of age diagnosed with type 2 diabetes (defined as HbA_{1c} 6.5 to 8.5% for patients receiving combination therapy with metformin and sulfonylurea or HbA_{1c} 7.0 to 10.0% for drug-naïve or patients receiving monotherapy), FPG of 126 to 270 mg/dL and BMI ≥ 27kg/m²; any subjects previously receiving metformin or metformin and sulfonylurea must have received \leqmetformin 1,000</p>	<p>N=766</p> <p>2-week wash out period followed by 4 to 7 weeks of run-in period and 24 weeks of treatment</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG at week 24, proportion of patients responding to treatment (reduction $\geq 0.7\%$ for HbA_{1c} and ≥ 30 mg/dL for FPG at week 24), clinical safety, adverse events, tolerability, clinical laboratory tests</p>	<p>Primary: After 24 weeks, RSG+MET and MET were both effective in improving HbA_{1c} with mean reductions of -0.93% (95% CI, -1.06 to -0.80) and -0.71% (95% CI, -0.83 to -0.60), respectively, with a mean treatment difference of -0.20% (95% CI, -0.36 to -0.04).</p> <p>Secondary: Significant reductions in FPG from baseline were seen in patients receiving RSG+MET (-2.29 mmol/L; 95% CI, -2.59 to -1.99) compared to patients receiving MET (-1.12 mmol/L; 95% CI, -1.43 to -0.82), with a treatment difference of -0.85 mmol/L (95% CI, -1.23 to -0.47).</p> <p>The proportion of patients who responded to treatment (reduction in HbA_{1c} $\geq 0.7\%$) was greater in the RSG+MET group than the MET group (59.5 and 49.5%, respectively) with the treatment difference of 10% (95% CI, 1.9 to 18.1).</p> <p>The proportion of FPG responders (reduction in FPG ≥ 30 mg/dL) was also greater in the RSG+MET group than in the MET group (55.0 vs 32.5%, respectively).</p> <p>The percentage of patients experiencing a gastrointestinal effect was greater in the MET group compared to the RSG+MET group (38.7 and 27.9%). The odds of experiencing a gastrointestinal side effect were 63% greater for patients receiving MET compared to patients receiving</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	mg/day for at least 3 months prior to study entry and patients must have stopped previous treatment with TZD at least 3 months prior to screening			<p>RSG+MET (OR, 1.63; 95% CI, 1.19 to 2.24).</p> <p>RSG+MET resulted in a mean weight gain of 1.79 kg (P<0.0001) compared to a mean weight loss of -1.78 kg (P<0.001) with MET.</p> <p>There were three deaths during the course of the study with two prior to DB study medication, and one while on RSG+MET; the cause of which was unknown, although it was not considered to be treatment related.</p>
<p>TODAY Study Group.⁸⁹ (2012) TODAY</p> <p>Metformin</p> <p>vs</p> <p>rosiglitazone 4 mg BID plus metformin</p> <p>vs</p> <p>metformin plus lifestyle intervention (focusing on weight loss through eating and activity behaviors)</p> <p>Patients were treated during a run-in period of 2 to 6 months with metformin 1,000 mg BID to attain</p>	<p>MC, RCT</p> <p>Patients 10 to 17 years of age, with type 2 diabetes</p>	<p>N=699</p> <p>3.86 years (average follow-up)</p>	<p>Primary: Loss of glycemic control (HbA_{1c} ≥8.0% for six months or sustained metabolic decompensation requiring insulin)</p> <p>Secondary: Body weight, metabolic outcomes, safety</p>	<p>Primary: Overall, a total of 319 (45.6%) patients reached the primary outcome, with a median time to treatment failure of 11.5 months (range, <1 to 66). Rates of failure were 51.7 (95% CI, 45.3 to 58.2), 38.6 (95% CI, 32.4 to 44.9), and 46.6% (95% CI, 40.2 to 53.0) of patients on metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention, respectively.</p> <p>Rosiglitazone plus metformin was more efficacious to metformin; combination therapy was associated with a 25.3% decrease in the occurrence of the primary outcome compared to metformin (P=0.006). The outcome with metformin plus lifestyle intervention was intermediate, but not significantly different from metformin or rosiglitazone plus metformin (P value not reported). The reasons for treatment failure did not differ significantly across treatments.</p> <p>Prespecified analyses according to sex and race or ethnic group showed differences in sustained effectiveness, with metformin least effective in non-Hispanic black patients and rosiglitazone plus metformin most effective in female patients.</p> <p>Secondary: BMI over time (up to 60 months) differed significantly according to the study treatment (P<0.001 for the overall comparison), and the results of all three pairwise comparisons between treatment groups were also significant. Patients treated with rosiglitazone plus metformin had the greatest increase in BMI and patients receiving metformin plus lifestyle intervention had the least.</p> <p>The change in fat mass from baseline differed significantly across the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>an HbA_{1c} <8.0% prior to randomization.</p>				<p>treatment groups (P<0.05) because of a significant difference between rosiglitazone plus metformin and metformin plus lifestyle interventions. There were no significant between-group differences in the change from baseline for any other outcome.</p> <p>Serious adverse events were reported in 19.2% of all patients, including 18.1, 14.6, and 24.8% with metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention (P=0.02). Hospitalizations accounted for more than 90% of serious adverse events. Severe hypoglycemia occurred in one, one, and two patients receiving metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention. No effects of rosiglitazone on bone mineral content or rate of fracture were noted.</p>
<p>Stewart et al.⁹⁰ (2006)</p> <p>Rosiglitazone 8 mg QD and metformin 2,000 mg/day (MET + RSG)</p> <p>vs</p> <p>metformin 3,000 mg/day (MET)</p>	<p>DB, MC, PG, RCT</p> <p>Type 2 diabetic patients 18 to 70 years of age, who were either antidiabetic-drug-naïve with FPG of 7.0 to 9.0 mmol/L and HbA_{1c} 7.0 to 9.0%, or previously treated with oral antidiabetic monotherapy with FPG 6.0 to 8.0 mmol/L and HbA_{1c} 6.5 to 8.0%</p>	<p>N=526</p> <p>32 weeks</p>	<p>Primary: Proportion of patients achieving HbA_{1c} ≤6.5% at week 32, change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving target HbA_{1c} and FPG levels, change in baseline FPG and fasting plasma insulin, change in insulin resistance, pancreatic β-cell function, CRP, lipid parameters and 24-hour ambulatory BP, safety</p>	<p>Primary: At week 32, there was a reduction from baseline in mean HbA_{1c} in the MET+RSG group from 7.2 to 6.7% compared to 7.2 to 6.8% in the MET group (P=0.0357).</p> <p>Secondary: The proportion of patients achieving HbA_{1c} ≤6.5% at week 32 was similar in the two groups (P=0.095).</p> <p>The proportion of patients achieving FPG <7.0 mmol/L at week 32 was 56% in the MET+RSG group compared to 38% in the MET group (OR, 2.33; P<0.0001).</p> <p>The reduction in fasting plasma insulin from baseline was greater in the MET+RSG group compared to the MET group (treatment difference, -12.2 pmol/L; P=0.00029).</p> <p>HOMA-S, β-cell function, CRP, and SBP were greater in the MET+RSG group at week 32 compared to the MET group (P<0.05 for all).</p> <p>TC, HDL-C, and LDL-C increased, FFAs decreased, and TG did not change in the MET+RSG group, whereas in the MET group there were decreases in TC, LDL-C, and TG, and increases in HDL-C and FFAs. The difference between the treatments was significant for the above parameters (P<0.05).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>The proportion of patients with reductions in 24-hour mean SBP was greater in the MET+RSG group compared to the MET group (treatment difference, -3.6 mm Hg; P=0.0315).</p> <p>The overall incidences of gastrointestinal adverse events were comparable between groups, but there was a lower incidence of diarrhea in the MET+RSG group (8 vs 18%). Hypoglycemia was reported in 17 patients (7%) in the MET+RSG group compared to 10 patients (4%) in the MET group.</p> <p>There were greater reductions in mean hemoglobin and hematocrit over 32 weeks in the MET+RSG group compared to the MET group (P<0.0001).</p>
<p>Rosak et al.⁹¹ (2005)</p> <p>Rosiglitazone 4 to 8 mg and metformin (existing therapy)</p>	<p>OS, PM</p> <p>Two studies in which type 2 diabetics on metformin therapy received rosiglitazone add-on therapy; baseline HbA_{1c} was 8.1% in both trials</p>	<p>N=11,014</p> <p>6 months</p>	<p>Primary: Change in baseline HbA_{1c}, FPG, body weight, and BP</p> <p>Secondary: Not reported</p>	<p>Primary: Addition of rosiglitazone significantly reduced HbA_{1c} from baseline (-1.3%; P<0.0001).</p> <p>Addition of rosiglitazone significantly reduced FPG from baseline (-47.0 mg/dL; P<0.0001).</p> <p>Significant reduction in BP from baseline (-7/-3 mm Hg; P<0.0001) was observed with rosiglitazone add-on therapy.</p> <p>Significant reduction in weight (-1.7 kg; P<0.0001) was observed with rosiglitazone add-on therapy.</p> <p>Most commonly reported adverse events were weight gain (0.16%) and edema (0.15%).</p> <p>Secondary: Not reported</p>
<p>Bailey et al.⁹² (2005)</p> <p>Rosiglitazone/metformin fixed dose combination</p>	<p>DB, MC, PG, RCT</p> <p>Patients with type 2 diabetes poorly controlled (FPG ≥126 to 216 mg/dL)</p>	<p>N=568</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline</p>	<p>Primary: Reductions in HbA_{1c} observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-0.22% difference between treatment groups; P=0.001).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>4/1,000 mg to 8/2,000 mg daily</p> <p>vs</p> <p>metformin 2,500 to 3,000 mg daily</p>	<p>with metformin alone or in combination with an insulin secretagogue or acarbose; baseline HbA_{1c} 7.4% for rosiglitazone add-on therapy and 7.5% for metformin; patients were excluded if they had been treated with a TZD or insulin, had unstable cardiovascular or cerebrovascular conditions, or had uncontrolled hypertension</p>		<p>FPG and insulin, proportion of patients who achieved HbA_{1c} and FPG targets</p>	<p>Reductions in FPG observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-18.3 mg/dL difference between treatment groups; P<0.001).</p> <p>Significant reduction in fasting insulin was observed with rosiglitazone add-on therapy compared to metformin monotherapy (-12.4 pmol/L difference between treatment groups; P=0.001).</p> <p>Greater proportion of patients on rosiglitazone add-on therapy (54%) reached HbA_{1c} targets (<7.0%) compared to those treated with metformin monotherapy (36%; OR, 2.42; P<0.001).</p> <p>Greater proportion of patients on rosiglitazone add-on therapy (32%) reached FPG targets (<126 mg/dL) compared to those treated with metformin monotherapy (8%; OR, 5.71; P<0.001).</p> <p>Higher rate of withdrawal due to adverse events with metformin monotherapy (8 vs 4%; no P value reported) was noted. Gastrointestinal disorders were the most commonly reported event that caused withdrawal in the metformin monotherapy group.</p>
<p>Rosenstock et al.⁹³ (2006)</p> <p>Rosiglitazone/metformin fixed dose combination 4/1,000 mg to 8/2,000 mg daily</p> <p>vs</p> <p>rosiglitazone 4 to 8 mg daily</p> <p>vs</p> <p>metformin 500 to</p>	<p>DB, MC, RCT</p> <p>Type 2 diabetics with HbA_{1c} >7.5 to 11.0%, with FPG ≤270 mg/dL who were previously treated with diet and exercise or had not been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening</p>	<p>N=468</p> <p>32 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving HbA_{1c} and FPG targets, change in baseline FPG, safety</p>	<p>Primary: Patients receiving rosiglitazone/metformin showed significant improvements in HbA_{1c} with a reduction of -2.3% compared to baseline vs -1.8% with patients receiving metformin (P<0.0008) and -1.6% with patients receiving rosiglitazone (P<0.0001).</p> <p>Secondary: Target HbA_{1c} ≤6.5 and <7.0% were achieved in more patients in the rosiglitazone/metformin group (60 and 77%) than in the metformin (39 and 57%) or rosiglitazone (35 and 58%) groups, respectively (P values not reported).</p> <p>The greatest mean decrease in FPG was seen with rosiglitazone/metformin (-74 mg/dL) and was significant compared to metformin (-50 mg/dL; P<0.0001) and rosiglitazone (-47 mg/dL; P<0.0001).</p> <p>Treatment was well tolerated with nausea, vomiting and diarrhea as the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2,000 mg daily				most commonly reported adverse events. Edema was comparable between rosiglitazone/metformin (6%) and rosiglitazone (7%) and lower with metformin.
Hamann et al. ⁹⁴ (2008) Rosiglitazone/ metformin FDC 4 mg/2,000 mg daily (RSG+MET) vs glibenclamide‡ 5 mg and metformin 2,000 mg or gliclazide* 80 mg and metformin 2,000 mg daily (SU+MET)	DB, PG, RCT Overweight patients (BMI ≥25 kg/m ²) with type 2 diabetes, HbA _{1c} 7.0 to 10.0%, who received metformin ≥850 mg/day for at least 8 weeks	N=596 52 weeks	Primary: Change in HbA _{1c} from baseline to week 52 Secondary: Change in FPG, β-cell function, insulin resistance, hypoglycemia, BP	Primary: At week 52, mean change in HbA _{1c} from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25). Secondary: Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095). The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs 0.055 HbA _{1c} %/year, respectively; P=0.0002). Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001). Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001). After 52 weeks, 24-hour diastolic and systolic ambulatory BP were reduced with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ambulatory BP (-2.9 mm Hg; P=0.0013), but not for systolic ambulatory BP (-2.6 mm Hg; P=0.0549).
Marre et al. ⁹⁵ (2009) LEAD-1 Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo vs	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥3 months, HbA _{1c} 7.0 to 11.0% (previously on oral	N=1,041 26 weeks	Primary: Change in baseline HbA _{1c} Secondary: Proportion of patients reaching HbA _{1c} (<7.0 and ≤6.5%), FPG (5.0 to ≤7.2 mmol/L), and PPG (10.0 mmol/L) targets;	Primary: After 26 weeks, HbA _{1c} decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; P<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; P<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; P<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; P<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were more efficacious compared to treatment with rosiglitazone (P<0.0001 for both measures). Decreases in HbA _{1c} were greater in patients previously on an oral glucose lowering agent monotherapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo plus glimepiride 2 to 4 mg/day</p> <p>vs</p> <p>placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day</p>	<p>glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤ 45 kg/m²</p>		<p>change in baseline body weight, FPG, mean PPG, β cell function, and BP</p>	<p>Secondary:</p> <p>The proportion of patients reaching HbA_{1c} targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached HbA_{1c} <7.0 and $\leq 6.5\%$ compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching HbA_{1c} targets were greater compared to patients receiving placebo (P<0.0001) and rosiglitazone (P<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (P=0.018).</p> <p>The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; P=0.002), 1.2 mg (37%; P<0.001), and 1.8 mg (38%; P=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively).</p> <p>The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported).</p> <p>Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported).</p> <p>Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P\leq0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Rosenstock et al.⁹⁶ (2006)</p> <p>Rosiglitazone/metformin fixed dose combination 4/1,000 mg to 8/2,000 mg daily</p>	<p>MC, OL</p> <p>Type 2 diabetics with HbA_{1c} >11.0% or FPG >270 mg/dL who were previously treated with diet and exercise or had not been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening</p>	<p>N=190</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients achieving HbA_{1c} targets; change in baseline FPG, lipids, and insulin sensitivity (HOMA-S)</p>	<p>Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported).</p> <p>Primary: Clinically significant mean reductions in HbA_{1c} (11.8 to 7.8%; P<0.0001) were observed after initiation of rosiglitazone/metformin at week 24.</p> <p>Secondary: Treatment goals of HbA_{1c} ≤6.5% and <7.0% at week 24 were achieved in 33 and 44% of patients, respectively.</p> <p>Clinically significant mean reductions in FPG (304 to 166 mg/dL; P<0.0001) were observed after initiation of rosiglitazone/metformin at week 24.</p> <p>HDL-C increased 4.4% and TC (-3.7%), LDL-C (-0.7%) and TG (-13.4%) decreased compared to baseline (P values not reported).</p> <p>Rosiglitazone/metformin significantly increased HOMA estimates of insulin sensitivity by 68% (P<0.0001).</p> <p>Rosiglitazone/metformin was well tolerated. There was a 2% incidence of hypoglycemia, mean increase in weight of 2.6 kg from baseline and 2.6% of patients withdrew because of an adverse event.</p>
<p>Fonseca et al.⁹⁷ (2003)</p> <p>Rosiglitazone 8 mg QD and nateglinide 120 mg before each meal</p> <p>vs</p> <p>rosiglitazone 8 mg QD and placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥21 years of age with type 2 diabetes for ≥6 months previously and treated with rosiglitazone 8 mg/day, diet, and exercise for ≥3 months, had a BMI 22 to 40 kg/m², FPG 6.1 to 13.3 mmol/L,</p>	<p>N=402</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, two-hour postprandial insulin, TC, LDL-C, HDL-C, TG, body weight, four-hour AUC for glucose, insulin during meal</p>	<p>Primary: HbA_{1c} did not change significantly from baseline in the placebo group, but did change significantly in the nateglinide group. The change from baseline to end point was -0.8±0.1% (P<0.0001 vs baseline or placebo).</p> <p>Secondary: Change in FPG decreased significantly from a baseline of 9.8 to 9.0 mmol/L in the nateglinide group (P<0.001). FPG did not change significantly from the baseline (10 mmol/L) in patients receiving placebo.</p> <p>Two-hour postprandial insulin in the nateglinide group decreased from 14.0 to 11.4 mmol/L (P<0.0001). The group receiving placebo had an increase in 2-hour postprandial insulin from 14.4 to 14.8 mmol/L</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	and HbA _{1c} 7.0 to 11.0%		challenges	<p>(P<0.0001 vs nateglinide).</p> <p>Total and incremental glucose AUC_{S(0-4 hours)} were significantly reduced in the nateglinide group (-8.6±0.8 and -6.2±0.5 mmol/L/hr, respectively; P<0.0001 vs baseline or placebo for both total and incremental AUCs). This represents a 16% reduction in the total and a 49% reduction in the incremental glucose AUC.</p> <p>Total and incremental insulin AUC_{S(0-4 hour)} were increased in the nateglinide group (425 and 395 pmol/L/hr, respectively; P<0.0001 vs baseline or placebo plus for both total and incremental AUCs). This represents a 46% increase in the total and 69% increase in the incremental insulin AUC.</p> <p>There were no significant changes in TC, LDL-C, or TG in either group. There was a small, but significant increase from baseline in HDL-C observed in patients receiving nateglinide (P<0.025) and in patients receiving placebo (P<0.005).</p> <p>Body weight increased in both groups. The mean change from baseline in patients receiving nateglinide (3.1±0.3 kg) was significantly greater compared to patients receiving placebo (1.1±0.3 kg; P<0.0001).</p> <p>Meal challenges were performed at week 0 and at end point. The glucose and insulin profiles were similar in the two groups at baseline, and PPG and insulin concentrations were unchanged at end point relative to baseline in patients receiving placebo.</p>
<p>Raskin et al.⁹⁸ (2004)</p> <p>Rosiglitazone 2 to 4 mg BID and repaglinide 0.5 to 4 mg TID before meals</p> <p>vs</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥18 years old with type 2 diabetes for ≥12 months with an HbA_{1c} >7.0 to ≤12.0% during previous monotherapy with</p>	<p>N=252</p> <p>24 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG</p>	<p>Primary: Mean change in HbA_{1c} from baseline with repaglinide was -0.17% and -0.56% with rosiglitazone. The mean change in HbA_{1c} from baseline with combination therapy was -1.43 (P≤0.001 vs either monotherapy). The reduction in HbA_{1c} from baseline was greater with combination therapy compared to the sum of the responses for monotherapy (P<0.01).</p> <p>Secondary: Mean FPG change from baseline with repaglinide was -3 mmol/L and -3.7 mmol/L with rosiglitazone. Mean FPG change from baseline with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone 2 to 4 mg BID vs repaglinide 0.5 to 4 mg TID before meals	sulfonylurea or metformin for ≥ 3 months with a BMI ≤ 45 kg/m ²			combination therapy was -5.2 mmol/L (P \leq 0.001 vs either monotherapy).
McCluskey et al. ⁹⁹ (2004) Rosiglitazone (existing therapy) and glimepiride 2 to 8 mg QD vs rosiglitazone (existing therapy)	MC, PC, RCT Patients with type 2 diabetes poorly controlled (HbA _{1c} 7.5 to 9.5%) with rosiglitazone monotherapy	N=40 30 weeks	Primary: Effect on HbA _{1c} Secondary: Effect on FPG, body weight, lipoproteins, proportion of patients who achieved HbA _{1c} and FPG targets	Primary: Significant reductions in HbA _{1c} were observed with glimepiride (-1.2%) compared to placebo (-0.3%; P<0.001). Secondary: Significant reductions in FPG were observed with glimepiride (-24.41 mg/dL) compared to placebo (5.9 mg/dL; P<0.008). Significantly greater proportion of patients receiving glimepiride achieved the target HbA _{1c} $\leq 7.0\%$ (60.0 vs 14.3%; P<0.008). There were no significant differences between treatment groups in TC, HDL-C, LDL-C, or TG at any time during study period.
Rosenstock et al. ¹⁰⁰ (2008) <u>Study A</u> Rosiglitazone 4 mg QD and glimepiride 3 mg QD (RSG 4 mg + GLIM) vs rosiglitazone 8 mg QD and	2 DB, PC, RCT Patients 40 to 80 years of age (Study A) or 18 to 75 years of age (Study B) with type 2 diabetes, HbA _{1c} $\geq 7.0\%$ and FPG 126 to 270 mg/dL at baseline; in the 3 months prior to enrolment, eligible patients in Study A received	N=174 (Study A) N=391 (Study B) 26 weeks (Study A) 24 weeks (Study B)	Primary: Mean change in baseline HbA _{1c} Secondary: Proportion of patients with HbA _{1c} <7.0% and/or HbA _{1c} reduction $\geq 0.7\%$ at the end of the treatment period, mean change in baseline FPG	<u>Study A</u> Primary: At week 26, the mean change in HbA _{1c} from baseline was -0.63% in the RSG 4 mg+GLIM (P=0.03 vs GLIM 3 mg), -1.17% in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -0.08% in the GLIM 3 mg group. Secondary: The mean change in FPG from baseline was -21 mg/dL in the RSG 4 mg+GLIM (P=0.09 vs GLIM alone), -43 mg/dL in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -2 mg/dL for GLIM 3 mg. At week 26, 43% of patients achieved HbA _{1c} <7.0% in the RSG 4 mg+GLIM group (P=0.0129 vs GLIM alone) and 68% achieved the same HbA _{1c} goal in the RSG 8 mg+GLIM group (P=0.0001 vs GLIM 3 mg)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>glimepiride 3 mg QD (RSG 8 mg + GLIM)</p> <p>vs</p> <p>glimepiride 3 mg QD (GLIM alone)</p> <p>Study B Rosiglitazone 4 mg QD and glimepiride 2 to 4 mg QD (RSG add-on)</p> <p>vs</p> <p>glimepiride 4 to 8 mg QD and placebo (GLIM)</p>	<p>monotherapy with an oral antidiabetic agent; eligible patients in Study B were treated with a non-TZD oral antidiabetic therapy for ≥ 3 months prior to screening, including metformin monotherapy, sulfonylurea monotherapy, or low-dose combination therapy with metformin and sulfonylurea</p>			<p>compared to 32% in the GLIM 3 mg.</p> <p>Study B Primary: At week 24, the mean change in HbA_{1c} from baseline was -0.68% in the RSG add-on group compared to -0.08% in the GLIM 4 to 8 mg group (P<0.0001).</p> <p>Secondary: The mean change in FPG from baseline was -28 mg/dL in the RSG add-on group compared to -1 mg/dL in the GLIM 4 to 8 mg group (P<0.0001).</p> <p>At week 24, 39% of patients achieved HbA_{1c} <7.0% in the RSG add-on group compared to 15% in the GLIM 4 to 8 mg group (P<0.0001).</p> <p>Insulin sensitivity increased significantly in the RSG add-on group but was unchanged with GLIM 4 to 8 mg. β-cell function increased over 24 weeks in both treatment groups but with a significantly greater increase with RSG add-on group.</p> <p>RSG add-on significantly reduced fasting levels of C-peptide (P=0.025), proinsulin (P=0.0006), and insulin (P=0.013) and reduced the proinsulin:insulin ratio (P<0.0001). There were no significant changes in any of these parameters with GLIM 4 to 8 mg (C-peptide; P=0.075, proinsulin; P=0.42, insulin; P=0.10 and proinsulin:insulin ratio; P=0.34).</p>
<p>Chou et al.¹⁰¹ (2008)</p> <p>Rosiglitazone/glimepiride fixed dose combination 4/1 mg titrated to 4/4 mg (regimen A) or titrated to 8/4 mg QD (regimen B) (RSG/GLIM)</p>	<p>DB, MC, PG, RCT</p> <p>Type 2 diabetics, HbA_{1c} 7.5 to 12.0%, fasting C-peptide ≥ 0.8 ng/mL, FPG ≥ 126 mg/dL, who had been treated with diet and/or exercise alone or who had not taken oral antidiabetic</p>	<p>N=901</p> <p>28 weeks</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, proportion of patients achieving HbA_{1c} and FPG targets, HOMA-S, HOMA-B, cardiovascular</p>	<p>Primary: Both rosiglitazone/glimepiride regimens significantly reduced HbA_{1c} to a greater extent than glimepiride or rosiglitazone monotherapy regimens (P<0.0001).</p> <p>Secondary: A significantly greater reduction in FPG levels was observed in the rosiglitazone/glimepiride group compared to the glimepiride or rosiglitazone monotherapy groups (P<0.0001).</p> <p>Significantly more patients achieved HbA_{1c} target levels ≤ 6.5 and <7.0% with either rosiglitazone/glimepiride regimen than patients with</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>rosiglitazone 4 mg titrated to 8 mg QD (RSG)</p> <p>vs</p> <p>glimepiride 1mg titrated to 4 mg QD (GLIM)</p>	<p>medication or insulin for >15 days in the preceding 4 months</p>		<p>biomarkers, safety</p>	<p>glimepiride or rosiglitazone monotherapy regimens (P<0.0001).</p> <p>Improvement in CRP was also observed in patients treated with rosiglitazone/glimepiride or rosiglitazone monotherapy compared to patients treated with glimepiride monotherapy (P<0.05).</p> <p>There were no new safety or tolerability issues identified from its monotherapy components and a similar adverse event profile was observed across the fixed-dose regimens. The most commonly reported adverse event was hypoglycemia and the incidence of confirmed symptomatic hypoglycemia (3.6 to 5.5%) was comparable among subjects treated with a fixed-dose regimen and glimepiride monotherapy.</p>
<p>Home et al.¹⁰² (2007)</p> <p>Rosiglitazone plus either metformin or a sulfonylurea</p> <p>vs</p> <p>metformin plus a sulfonylurea</p>	<p>MC, OL, PG, RCT</p> <p>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m², on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)</p>	<p>N=1,122</p> <p>18 months</p>	<p>Primary: Change in baseline HbA_{1c}</p> <p>Secondary: FPG, serum lipids, HOMA basal insulin sensitivity and islet β-cell function (HOMA %β), body weight, inflammatory/thrombotic markers, CRP</p>	<p>Primary: At 18 months, HbA_{1c} reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference, 0.07%; 95% CI, -0.09 to 0.23; P value not significant), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference, 0.06%; 95% CI, -0.09 to 0.20; P value not significant).</p> <p>Secondary: Differences in FPG were not significant at 18 months (rosiglitazone vs sulfonylurea, -0.36 mmol/L; P=0.062 and rosiglitazone vs metformin, -0.34 mmol/L; P=0.089).</p> <p>Rosiglitazone increased TC (P≤0.001) and LDL-C (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared to the control. An increase in HDL-C and TG was observed with rosiglitazone compared to sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001, 0.40 vs 0.15 mmol/L; P=0.016, respectively), but not with metformin (P value not significant for both).</p> <p>HOMA-estimated basal insulin sensitivity was substantially increased with rosiglitazone compared to the respective controls (P<0.001 for both). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, to a similar extent (P value not significant).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Rosiglitazone was associated with a significant increase in body weight compared to metformin (P<0.001) and a sulfonylurea (P=0.003).</p> <p>At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to sulfonylureas (-5.7 vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P value not significant).</p> <p>There was a significant reduction in CRP with rosiglitazone compared to a sulfonylurea (P<0.001) and metformin (P=0.001).</p>
<p>Komajda et al.¹⁰³ (2008)</p> <p>Rosiglitazone plus either metformin or a sulfonylurea</p> <p>vs</p> <p>metformin plus a sulfonylurea</p>	<p>MC, OL, RCT (RECORD)</p> <p>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m², on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)</p>	<p>N=668</p> <p>12 months</p>	<p>Primary: Change from baseline in 24-hour ambulatory BP at six months and 12 months</p> <p>Secondary: Not reported</p>	<p>Primary: For patients receiving rosiglitazone and a sulfonylurea, the reduction in 24-hour SBP was greater at six months (-3.8 mm Hg) and 12 months (-3.8 mm Hg) than with metformin and sulfonylurea therapy (-1.2 mm Hg and -1.3 mm Hg, respectively; six months, P=0.015; 12 months, P=0.031).</p> <p>Reductions in 24-hour DBP were greater at six months and 12 months for patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mm Hg) compared to metformin and sulfonylurea (-0.4 mm Hg and -0.6 mm Hg; both P<0.001).</p> <p>At 12 months, the reduction in 24-hour SBP was greater for rosiglitazone and metformin (-4.9 mm Hg) than for metformin and sulfonylurea (-2.2 mm Hg; P=0.016).</p> <p>At 12 months, the reduction in DBP was greater for rosiglitazone and metformin (-3.8 mm Hg) than for metformin and sulfonylurea (-1.7 mm Hg; P=0.003).</p> <p>At six months, the reductions in SBP and DBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (SBP; P=NS, DBP; P=0.049).</p> <p>Secondary: Not reported</p>
<p>Scott et al.¹⁰⁴</p>	<p>AC, DB, MC, PG,</p>	<p>N=273</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2008)</p> <p>Rosiglitazone 8 mg once daily and metformin (existing therapy)</p> <p>vs</p> <p>sitagliptin 100 mg once daily and metformin (existing therapy)</p> <p>vs</p> <p>metformin (existing therapy) and placebo</p>	<p>RCT</p> <p>Type 2 diabetics 18 to 75 years of age receiving stable metformin doses ($\geq 1,500$ mg/day for ≥ 10 weeks) and inadequate glycemic control ($HbA_{1c} \geq 7.0$ and $\leq 11.0\%$)</p>	<p>18 weeks</p>	<p>Change in baseline HbA_{1c}</p> <p>Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, β cell function, insulin resistance, and lipid profile</p>	<p>Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.50%; 95% CI, -0.87 to -0.60; $P \leq 0.001$). Similar results were observed with rosiglitazone (treatment difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). There was no difference between sitagliptin and rosiglitazone (treatment difference, -0.06%; 95% CI, -0.25 to 0.14).</p> <p>The proportion of patients achieving an $HbA_{1c} < 7.0\%$ was significantly greater with sitagliptin (55%; $P = 0.006$) and rosiglitazone (63%; P value not reported) compared to placebo (38%). There was no difference between sitagliptin and rosiglitazone (treatment difference, 8%; 95% CI, -6 to 22; P value not reported).</p> <p>Secondary: Sitagliptin (treatment difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; $P \leq 0.001$) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo.</p> <p>Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported).</p> <p>Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; $P \leq 0.05$) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported).</p> <p>Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported).</p> <p>Rosiglitazone significantly decreased fasting serum insulin compared to</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>placebo (treatment difference, -3.4 μIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 μIU/mL; 95% CI, -5.50 to -1.40; P value not reported).</p> <p>The proinsulin:insulin ratio was similar across all treatments.</p> <p>Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; $P \leq 0.05$) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin (treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; $P \leq 0.05$) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported).</p>
<p>Rigby et al.¹⁰⁵ (2010)</p> <p>Rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy)</p> <p>vs</p> <p>sitagliptin 100 mg QD and metformin (existing therapy)</p> <p>vs</p> <p>colesevelam 3.75 g</p>	<p>OL</p> <p>Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control (HbA_{1c} 6.5 to 10.0% on a stable regimen of metformin (1,500-2,550 mg daily), with LDL-C \geq60 mg/dL and TG <500 mg/dL</p>	<p>N=169</p> <p>16 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 16</p> <p>Secondary: Change in HbA_{1c} from baseline to week eight, change in fasting plasma glucose and fasting insulin from baseline to weeks eight and 16, change in two-hour PPG and postprandial insulin after a meal</p>	<p>Primary: At week 16, HbA_{1c} was reduced from baseline in all treatment groups (least square mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; $P=0.031$); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; $P<0.001$); sitagliptin -0.4% (95% CI, -0.64 to -0.13; $P=0.009$).</p> <p>Secondary: At week eight, HbA_{1c} was reduced from baseline with colesevelam and sitagliptin (-0.3%; $P=0.006$ and -0.5%; $P<0.001$, respectively), but not with rosiglitazone (-0.2%; $P=0.109$).</p> <p>Fasting plasma glucose was significantly reduced from baseline at week eight and week 16 in all treatment groups.</p> <p>The two-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups.</p> <p>There was no significant change in fasting insulin or two-hour</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily (QD or BID) and metformin (existing therapy)			tolerance test, change in lipid parameters, percentage of participants who achieved an HbA _{1c} reduction >0.7% from baseline, percentage of participants who achieved HbA _{1c} <7.0%	<p>postprandial insulin from baseline to week 16 in any treatment group.</p> <p>Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008).</p> <p>LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011).</p> <p>TC levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median TG levels increased significantly from baseline with colesevelam (P<0.001) and rosiglitazone (P<0.001); however, sitagliptin did not significantly affect triglyceride levels. HDL-C levels did not change significantly from baseline with any treatment.</p> <p>At week 16, 23.2% of patients in the colesevelam group, 48.1 % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in HbA_{1c} 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved HbA_{1c} <7.0%.</p> <p>The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in severity.</p>
Hollander et al. ¹⁰⁶ (2009) Thiazolidinedione (existing therapy) and saxagliptin 2.5 mg QD	DB, MC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA _{1c} ≥7.0 to	N=565 24 weeks	Primary: Change in baseline HbA _{1c} Secondary: Change in baseline FPG and PPG	Primary: Saxagliptin significantly decreased HbA _{1c} compared to placebo (saxagliptin 2.5 mg, -0.66%; treatment difference, -0.36%; P<0.0007 vs placebo and saxagliptin 5 mg, -0.94%; treatment difference, -0.63%; P<0.0001 vs placebo). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>thiazolidinedione (existing therapy) and saxagliptin 5 mg QD</p> <p>vs</p> <p>thiazolidinedione (existing therapy) and placebo</p>	<p>≤10.5%) receiving stable doses of TZD (pioglitazone 30 or 45 mg/day or rosiglitazone 4 or 8 mg/day for ≥12 weeks), fasting C-peptide ≥0.3 nmol/L, and BMI ≤45 kg/m²</p>		<p>AUC_{0-3hr}, proportion of patients achieving an HbA_{1c} <7.0%</p>	<p>Saxagliptin significantly decreased FPG compared to placebo (saxagliptin 2.5 mg treatment difference, -0.8 mmol/L; P<0.0053 vs placebo and saxagliptin 5 mg treatment difference, -1.0 mmol/L; P=0.0005 vs placebo).</p> <p>A significantly greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (42.2 [P=0.0010] and 41.8 [P=0.0013] vs 25.6%).</p> <p>Saxagliptin significantly decreased PPG AUC_{0-3hr} compared to placebo (P<0.0001 for both). Similar results were observed with PPG AUC_{0-2hr} (P<0.0001 for both).</p> <p>Overall, saxagliptin was well tolerated. The proportion of patients experiencing any adverse effect was 68.0 vs 66.8%, with the highest frequency with saxagliptin 5 mg. The frequency of hypoglycemic events was similar between the two treatments (3.4 vs 3.8%). The most commonly reported adverse events were upper respiratory tract infection, peripheral edema, and headache.</p>
<p>Pinelli et al.¹⁰⁷ (2008)</p> <p>Thiazolidinediones in combination with other antidiabetic agents</p> <p>vs</p> <p>exenatide in combination with other antidiabetic agents</p>	<p>MA (22 RCTs)</p> <p>Patients with type 2 diabetes receiving combination therapy</p>	<p>N=9,325</p> <p>≥24 weeks</p>	<p>Primary: Mean change in baseline HbA_{1c}</p> <p>Secondary: Proportion of patients reaching HbA_{1c} <7.0%, mean change from baseline in FPG and body weight, hypoglycemia, gastrointestinal adverse events</p>	<p>Primary: There were small reductions in HbA_{1c} across the trials. The WMD were -0.80% (95% CI, -1.10 to -0.50) with TZD and -0.60% (95% CI, -1.04 to -0.16) with exenatide.</p> <p>When only PC trials were analyzed, there were greater reductions in HbA_{1c} with both TZDs (WMD, -1.14%; 95% CI -1.30 to -0.98) and exenatide (WMD, -0.97%; 95% CI -1.11 to -0.83).</p> <p>When only TZD AC trials were analyzed, there was a significant difference in HbA_{1c} levels from baseline (WMD, -0.38%; 95% CI -0.75 to -0.01).</p> <p>There was no difference in HbA_{1c} reduction between exenatide and insulin comparators in OL, non-inferiority trials.</p> <p>Secondary: TZD and exenatide-based therapies were associated with OR of 2.27 (95%</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>CI, 1.22 to 4.24) and 2.90 (95% CI, 1.28 to 6.55), respectively, for reaching HbA_{1c} <7.0%.</p> <p>FPG concentrations were reduced from baseline with TZD-based regimens (WMD, -29.58 mg/dL; 95% CI, -39.27 to -19.89), but did not reach significance with exenatide (WMD, -8.77 mg/dL; 95% CI, -28.85 to 11.31).</p> <p>Severe hypoglycemia was rare in the one exenatide and four TZD trials that identified a total of nine participants experiencing hypoglycemic episodes. In these five trials, participants reporting an event were also receiving an insulin secretagogue. The OR for developing nonsevere hypoglycemia with TZDs was not significantly different from other treatment arms (OR, 1.59; 95% CI, 0.76 to 3.32).</p> <p>In TZD trials, there was a nonsignificant difference in body weight from baseline compared to other treatment groups (WMD, 1.51 kg; 95% CI, -0.12 to 3.15). Mean change in body weight from baseline was reduced significantly with exenatide-based regimens (WMD, -2.74 kg; 95% CI, -4.85 to -0.64).</p> <p>The most commonly reported adverse effects were gastrointestinal disorders in the exenatide trials. ORs greater than one for nausea, vomiting, and diarrhea were observed with exenatide with pooled ORs of 9.02 (95% CI, 3.66 to 22.23), 4.56 (95% CI, 3.13 to 6.65), and 2.96 (95% CI, 2.05 to 4.26), respectively. Nausea occurred in 47% of patients receiving exenatide and 11% in the comparator arms. Vomiting occurred in 15% of patients receiving exenatide and 4% of patients receiving comparator. Diarrhea occurred in 12% of patients receiving exenatide and 4% in patients receiving comparator.</p>
<p>Clar et al.¹⁰⁸ (2009)</p> <p>Pioglitazone</p> <p>vs</p>	<p>MA</p> <p>Patients with type 2 diabetes</p>	<p>N=3,092 (8 trials)</p> <p>≥12 weeks</p>	<p>Primary:</p> <p>HbA_{1c}, frequency of hypoglycemia, total daily dose of insulin, weight changes, changes in</p>	<p>Primary:</p> <p>HbA_{1c} values were significantly lower in the groups taking pioglitazone plus insulin than in the groups taking insulin without pioglitazone (weighted mean difference -0.58%, 95% CI: -0.70 to -0.46; P<0.00001).</p> <p>There were more patients with hypoglycemic episodes in the pioglitazone plus insulin groups than with insulin without pioglitazone; however, this</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>no additional treatment</p> <p>All patients were receiving insulin (with or without other oral hypoglycemic agents).</p>			<p>cardiovascular risk factors, and adverse events</p> <p>Secondary: Not reported</p>	<p>difference was not statistically significant (relative risk 1.27, 95% CI: 0.99 to 1.63, P=0.06).</p> <p>Insulin dose ranged between 42 to 64 U/day or 0.5 to 1 U/kg/day in the pioglitazone groups and between 55 to 70 U/day and 0.7 to 1.2 U/kg/day in the groups taking no pioglitazone.</p> <p>Weight change ranged between +1.4 and +4.4 kg in the pioglitazone plus insulin groups and between -0.04 and +4.9 kg in the insulin only groups.</p> <p>Four studies reported results for serum TGs. Only two of the studies demonstrated a significant reduction in the pioglitazone groups (-0.44 to -0.70 mmol/L) compared to insulin only). None of the studies found a difference in TC between the pioglitazone plus insulin and the insulin without pioglitazone groups. Four studies reported on HDL-C and all found significantly increased values in the pioglitazone groups (+0.10 mmol/L to +0.18 mmol/L) compared to insulin only. None of the studies found a difference in LDL-C between the pioglitazone plus insulin and the insulin without pioglitazone groups.</p> <p>Besides weight gain and hypoglycemia, the only adverse event reported as occurring more frequently with pioglitazone was peripheral edema.</p>
<p>Abdul-Ghani et al.¹⁰⁹ (2015) EDICT</p> <p>Metformin (escalating dose)</p> <p>vs</p> <p>Triple therapy (metformin/pioglitazone/exenatide)</p>	<p>OL, RCT</p> <p>Drug-naïve, recently diagnosed (<2 years) subjects 30 to 75 years of age with type 2 diabetes mellitus</p>	<p>N=221</p> <p>2 years</p>	<p>Primary: HbA_{1c}</p> <p>Secondary: Percentage of participants achieving HbA_{1c} <6.5 and <7.0%; decrease in fasting and postprandial plasma glucose; change in body weight; and rate of hypoglycaemic events</p>	<p>Primary: Baseline HbA_{1c} was identical in both groups (8.6%) and during the first six months decreased in both treatment arms. At six months, there was a small but significant HbA_{1c} difference (0.2%, P=0.03) between groups (triple therapy 6.0% vs metformin therapy 6.2%). After six months, HbA_{1c} gradually increased with metformin therapy to 6.5% at 24 months and remained stable at 5.95% with triple therapy; thus, the difference in HbA_{1c} between the two treatments progressively increased with time and was significantly different at two years (change in HbA_{1c}, 0.55%; P<0.0001).</p> <p>Secondary: More participants receiving metformin therapy failed to maintain the treatment goal (HbA_{1c} <6.5%) than did those receiving triple therapy (44 vs 17%; P=0.003). A total of 40 participants receiving metformin therapy failed to maintain HbA_{1c} at <6.5% at/after six months compared with only</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>13 participants receiving triple therapy (P<0.0001). More participants receiving triple therapy (61%) had HbA_{1c} reduced to the normal range (<6.0%) than those receiving metformin therapy (27%; P<0.0001). The median HbA_{1c} of participants receiving triple therapy was 5.9% compared with 6.4% for those receiving metformin therapy. More than 90% of participants receiving triple therapy maintained HbA_{1c} at <7.0% versus <75% of participants receiving metformin therapy.</p> <p>The most common adverse event was hypoglycaemia, reported by 46 and 14% of participants receiving metformin and triple therapy, respectively. The overall frequency of hypoglycaemic events was greater in participants receiving metformin therapy (2.2 vs 0.31 events/participant per year; P<0.0001).</p>
<p>Hollander et al.¹¹⁰ (2015)</p> <p>Insulin glargine+ one oral antidiabetes drug (metformin or sulfonylurea) wherein previous TZD therapy was dropped and replaced with insulin glargine (GLAR +1 OAD)</p> <p>vs</p> <p>three oral antidiabetes drugs (3OAD) wherein patients receiving TZD and metformin received add-on</p>	<p>MC, OL, RCT</p> <p>Type 2 diabetes patients 18 to 79 years of age with a HbA_{1c} of 7.5 to 12.0% despite ≥3 months of treatment with a TZD plus metformin or a sulfonylurea</p>	<p>N=337</p> <p>48 weeks</p>	<p>Primary: Change in HbA_{1c}</p> <p>Secondary: Changes in FPG, weight, BMI, and serum lipid profile</p>	<p>Primary: Substitution of insulin glargine for a TZD and addition of a third OAD resulted in an adjusted mean change in HbA_{1c} from baseline of -1.66% and -1.86%, respectively (adjusted mean difference 0.20; 95% CI, -0.11 to 0.51). The upper limit of the 95% CI for the difference in the adjusted mean changes from baseline to endpoint for HbA_{1c} was 0.51%; therefore, the primary efficacy analysis did not demonstrate equivalent glycemic control during treatment with GLAR + 1 OAD and 3OAD as measured by HbA_{1c} levels. In patients originally taking sulfonylurea, there was a significantly greater reduction in HbA_{1c} in those adding metformin to TZD and sulfonylurea versus those switching the TZD for GLAR + SU at weeks 12, 24, and 48.</p> <p>Secondary: Adjusted mean FPG at baseline was similar between the two treatment arms (GLAR + 1 OAD 193.0 mg/dL vs 3OAD 199.5 mg/dL; P=0.4299). FPG reduced significantly from baseline to endpoint (P<0.0001 for both arms).</p> <p>Weight gain was observed in both treatment arms at each study visit and at endpoint. At each visit, patients in the GLAR + 1 OAD arm gained less weight than those in the 3OAD arm; this difference was significant at week 12 (P=0.0035). A similar pattern was observed for BMI.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>sulfonylurea (glyburide) and patients receiving TZD and sulfonylurea received add-on metformin (3OAD)</p>				<p>Overall, insulin glargine + metformin was as effective as 3OAD in achieving glycemic control but with greater improvements in lipid parameters, less weight gain, and lower hypoglycemia rates.</p>
<p>Schernthaner et al.¹¹¹ (2015) EUREXA</p> <p>TZD or glimepiride added to metformin plus exenatide twice daily</p> <p>vs</p> <p>exenatide twice daily added to metformin plus glimepiride</p>	<p>MC, OL, RCT</p> <p>Patients with type 2 diabetes with metformin failure (HbA_{1c} ≥6.5 to ≤9.0%), were 19 to 85 years of age, and had a BMI of ≥25 to ≤40 kg/m²</p>	<p>N=310</p> <p>Median duration of 2 years</p>	<p>Primary: Changes in HbA_{1c}, BMI, lipids, hypoglycaemia, and vital signs</p> <p>Secondary: Not reported</p>	<p>Primary: Significant changes from baseline in HbA_{1c} were observed at 52, 78, 104 and 130 weeks with add-on TZD (all P<0.01), but only at 52 weeks with add-on glimepiride (P=0.001). Significant between-group differences favouring add-on TZD were observed at 78 (P=0.004) and 130 weeks (P=0.001).</p> <p>Among patients re-randomized to add-on glimepiride and add-on TZD, HbA_{1c} ≤7.0% was achieved by 26.0 and 30.7%, respectively, and HbA_{1c} ≤6.5% by 8.2 and 9.3%, respectively (no significant differences between the randomized groups).</p> <p>BMI significantly increased from baseline at 52, 78, 104 and 130 weeks with add-on TZD (all P<0.01), but significantly increased at 52 and 78 weeks (both P<0.05) and decreased at 130 weeks with add-on glimepiride; the between-group difference was significant at 104 (P=0.022) and 130 weeks (P=0.008).</p> <p>HDL cholesterol significantly increased from baseline to 130 weeks in the TZD add-on group (P<0.001), but not in the add-on glimepiride group; the between-group difference significantly favoured TZD (P<0.001). For total and LDL cholesterol, there were no significant within- or between-group changes from baseline to 130 weeks.</p> <p>Systolic blood pressure was significantly increased at 130 weeks with add-on TZD (P=0.043), but not with add-on glimepiride; the between-group difference significantly favoured glimepiride (P=0.044).</p> <p>The incidence of any hypoglycaemia and nocturnal, non-nocturnal and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>documented symptomatic hypoglycaemia with blood glucose ≤ 70 mg/dl was significantly higher for glimepiride than TZD as add-on to exenatide plus metformin. Although the proportion of patients reporting documented symptomatic hypoglycaemia with blood glucose < 50 mg/dl was similar in the add-on glimepiride (1/74; 1.4%) or TZD (1/76; 1.3%) groups, the exposure-adjusted mean rate/year was higher in the glimepiride group (0.10 vs 0.01 events/year of patient exposure).</p> <p>Secondary: Not reported</p>
<p>Kheirbek et al.¹¹² (2013)</p> <p>Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use</p>	<p>OS, RETRO</p> <p>Veterans with diabetes cared for at a Veterans Administration Capital area medical center</p>	<p>N=17,773</p> <p>Variable duration</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Not reported</p>	<p>Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions.</p> <p>Secondary: Not reported</p>
<p>Mearns et al.¹¹³ (2015)</p> <p>Hypoglycemic</p>	<p>Network MA (62 RCTs)</p> <p>Patients with</p>	<p>N=32,185</p> <p>3 to 12 months</p>	<p>Primary: Changes in HbA_{1c}, body weight, and SBP; risk of</p>	<p>Primary: All agents significantly reduced HbA_{1c} vs placebo; although not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)</p>	<p>inadequately controlled type 2 diabetes on metformin alone</p>		<p>developing hypoglycemia and urinary and genital tract infection</p> <p>Secondary: Not reported</p>	<p>hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03).</p> <p>Secondary: Not reported</p>
Diabetes Prevention Trials				
<p>Zinman et al.¹¹⁴ (2010) CANOE</p> <p>Rosiglitazone 2 mg/day plus metformin 500 mg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, RCT</p> <p>Patients with impaired glucose tolerance</p>	<p>N=207</p> <p>3.9 years (median duration)</p>	<p>Primary: Time to development of diabetes</p> <p>Secondary: Insulin sensitivity, β cell function, safety</p>	<p>Primary: Incident diabetes occurred in significantly fewer patients receiving combination therapy compared to placebo (14 vs 39%; P<0.0001). The relative risk reduction was 66% (95% CI, 48 to 80) and the absolute risk reduction was 26% (95% CI, 14 to 37), yielding a number needed to treat of 4 (95% CI, 2.70 to 7.14).</p> <p>Seventy patients (80%) receiving combination therapy regressed to normal glucose tolerance compared to 52 patients (53%) receiving placebo (P=0.0002).</p> <p>Secondary: Insulin sensitivity decreased by trial end in patients receiving placebo (median, -1.24) and remained unchanged in patients receiving combination therapy (median, -0.39; P=0.0006 vs placebo).</p> <p>Change in β cell function did not differ between the two treatments (P=0.28).</p> <p>Significantly more patients receiving combination therapy experienced diarrhea compared to placebo (P=0.0253).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Gerstein et al.¹¹⁵ (2006) DREAM</p> <p>Rosiglitazone 4 mg once daily for 2 months, then 8 mg once daily</p> <p>vs</p> <p>placebo</p>	<p>MC, PRO, RCT</p> <p>Adults ≥ 30 years of age or more with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease; people with a history of diabetes (except gestational diabetes), cardiovascular disease or intolerance to either angiotensin-converting enzyme inhibitors or TZDs were excluded</p>	<p>N=5,269</p> <p>Median 3 years (range, 2.5 to 4.7 years)</p>	<p>Primary: Composite of incident diabetes or death</p> <p>Secondary: Regression to normoglycemia, composite of cardiovascular events (e.g., MI, stroke, cardiovascular death, revascularization procedures and heart failure) and glucose concentrations</p>	<p>Primary: The composite primary outcome was observed in 11.6% of individuals given rosiglitazone and 26.0% of individuals given placebo (HR, 0.40; 95% CI, 0.35 to 0.46; P<0.0001). There was no difference in the number of deaths (HR, 0.91; 95% CI, 0.55 to 1.49; P=0.7). The frequency of diabetes was reported in significantly fewer patients receiving rosiglitazone than those receiving placebo (HR, 0.38; 95% CI, 0.33 to 0.44; P<0.0001).</p> <p>Secondary: Normoglycemia was reported in 1,330 (50.5%) individuals in the rosiglitazone group and 798 (30.3%) participants in the placebo group (HR, 1.71; 95% CI, 1.57 to 1.87; P<0.0001).</p> <p>The frequency of composite cardiovascular outcome was similar between rosiglitazone and placebo. The components of the composite were similar between the two groups with the exception of heart failure, which was reported in 14 (0.5%) participants in the rosiglitazone group and two (0.1%) participants in the placebo group (P=0.01).</p> <p>The median fasting plasma glucose concentration was 0.5 mmol/L lower in the rosiglitazone group than in the placebo group (P<0.0001); the two-hour plasma glucose concentration was 1.6 mmol/L lower with rosiglitazone than placebo (P<0.0001).</p>
<p>Dagenais et al.¹¹⁶ (2008) DREAM</p> <p>Rosiglitazone 4 mg once daily for 2 months, then 8 mg once daily</p> <p>vs</p> <p>placebo</p>	<p>MC, PRO, RCT</p> <p>Adults ≥ 30 years of age with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease</p>	<p>N=5,269</p> <p>3 years</p>	<p>Primary: Composite cardiovascular outcome, composite renal outcome</p> <p>Secondary: Not reported</p>	<p>Primary: During the three year follow-up, 836 patients had a first occurrence of the composite cardiorenal outcome (2.5% cardiovascular composite outcomes and 13.6% renal composite outcomes).</p> <p>The composite cardiorenal outcome occurred in 15.0% of patients receiving rosiglitazone and 16.8% of patients receiving placebo (HR, 0.87; 95% CI, 0.75 to 1.01; P=0.07).</p> <p>Rosiglitazone did not reduce the overall risk of cardiovascular events, but significantly increased the risk for heart failure (0.5%) compared to placebo (0.1%; 95% CI, 1.60 to 31.0).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Rosiglitazone reduced the renal component of the composite outcome by 20% due to a reduction in progression of albuminuria compared to placebo (HR, 0.80; 95% CI, 0.68 to 0.93; P=0.031). The fall in estimated glomerular filtration rate by $\geq 30\%$ was not significant (P=0.087).</p> <p>Secondary: Not reported</p>

*Not available in the United States.

†Estimates approximate values since results were displayed in bar graph and precise values were not reported.

‡Synonym for glyburide.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, TID=three times daily

Study design abbreviations: AC=active-comparator, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PM=post marketing, PRO=prospective, RCT=randomized-controlled trial, RETRO=retrospective, SR=systematic review, XO=cross-over

Miscellaneous abbreviations: ALT=alanine aminotransferase, apo=apolipoprotein, AUC=area under the curve, BMD=bone mineral density, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA=homeostasis model assessment, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, HR=hazard ratio, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MACE=major adverse cardiovascular events, MI=myocardial infarction, NPH=neutral protamine Hagedorn, NYHA=New York Heart Association, OR=odds ratio, PGWB=psychological general well-being, PPAR=peroxisome proliferator-activated receptor, PPG=post-prandial glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TZD=thiazolidinedione, VLDL=very low density lipoprotein cholesterol, WMD=weighted mean difference

Additional Evidence

Dose Simplification

Vanderpoel et al. investigated the adherence rates with the fixed-dose combination of rosiglitazone and metformin compared to monotherapy or concomitant administration of the individual components. Prescription claims for 16,929 type 2 diabetics were analyzed for a 12-month time period. Adherence pre- and post-index was measured by a medication possession ratio, a proxy measurement to determine adherence. Compared to the pre-index period for concomitant administration of the individual components, the fixed-dose combination product had a significant increase in the medication possession ratio (+4.8; P<0.005). There was no significant difference in pill burden, insulin use rate, or non-study oral hyperglycemic agents between the two groups.¹¹⁷

Stable Therapy

Berhanu et al. evaluated changes in lipid profiles in 305 patients with type 2 diabetes and dyslipidemia after treatment conversion from rosiglitazone to pioglitazone with continuation of statin and other lipid-lowering therapies. At 17 weeks after treatment conversion from rosiglitazone to pioglitazone, patients had significant reductions in triglycerides (-15.2%; P<0.0001), total cholesterol (-9.0%; P<0.0001), and low-density lipoprotein (LDL) particle concentration (-189 nmol/L; P<0.0001) without significant changes in HbA_{1c} (0.02%). LDL cholesterol (+2.2%), high-density lipoprotein cholesterol (+1.8%; P<0.05), and LDL particle diameter (+0.23 nm; P<0.0001) increased as well.¹¹⁸

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 15. Relative Cost of the Thiazolidinediones

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Pioglitazone	tablet	N/A	N/A	\$
Rosiglitazone	tablet	Avandia®	\$\$\$\$	N/A
Combination Products				
Pioglitazone and glimepiride	tablet	Duetact®*	\$\$\$\$\$	\$\$\$\$\$
Pioglitazone and metformin	tablet	Actoplus Met XR®	\$\$\$\$\$	\$\$\$

*Generic is available in at least one dosage form or strength.

N/A=Not available

X. Conclusions

The thiazolidinediones are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹⁻⁶ Pioglitazone, pioglitazone-glimepiride, and pioglitazone-metformin are available in generic formulations. Metformin and glimepiride are also available generically in separate formulations.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The thiazolidinediones are noted to be associated with weight gain, fluid retention, congestive heart failure, and fractures. The thiazolidinediones are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. However, due to the mechanisms of action of the thiazolidinediones and metformin, the addition of an incretin mimetic, dipeptidyl peptidase-4 (DPP-4) inhibitor, or secretagogue is preferred over a thiazolidinedione to be added to metformin. In addition, the combination of metformin and a thiazolidinedione, while efficacious, carries risks of adverse events associated with both agents. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, an SGLT2 inhibitor, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. In general, recommendations regarding the thiazolidinediones are made for the medication class as a whole; however, more recent guidelines from the American Diabetes Association/European Association for the Study of Diabetes do not recommend rosiglitazone.⁷⁻¹⁹

A variety of clinical trials have been conducted with the thiazolidinediones.²¹⁻¹¹⁶ In comparative studies, the use of pioglitazone and rosiglitazone led to similar improvements in glycemic control.^{42,43,45,47,48,62} Several studies evaluated the efficacy of thiazolidinediones in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.^{68-71,88-90,97-100,106} However, in studies that directly compared various dual therapy regimens, there were no differences in efficacy noted.^{72-81,94,102,104} The thiazolidinedione fixed-dose combination products have been shown to improve glycemic control in patients with type 2 diabetes.^{70,92-94,96,101} However, there were no randomized studies found in the medical literature that directly compared the efficacy of the fixed-dose combination products to the coadministration of each component as separate formulations.

Thiazolidinediones may cause weight gain and fluid retention, as well as increase the risk for congestive heart failure and fractures.¹⁻⁶ The cardiovascular safety of rosiglitazone has been a controversial issue since 2007. The results of two cardiovascular outcomes studies with the thiazolidinediones have been reported (PROactive and RECORD); however, neither study directly compared pioglitazone and rosiglitazone.^{21,28} A variety of meta-analyses have been conducted by independent investigators to assess the link between the use of thiazolidinediones and cardiovascular events.³⁰⁻³⁷ Previously, prescribing information for pioglitazone and rosiglitazone differed with regards to myocardial ischemic events. In November 2013, the FDA announced the removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010. This decision was based partly on a re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial²⁷ conducted by the Duke Clinical Research Institute²⁹, which determined that recent data for rosiglitazone-containing drugs do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylurea. Under these modifications, distribution of rosiglitazone-containing products is no longer restricted. Health care professionals, pharmacies, and patients will no longer be required to enroll in the rosiglitazone Risk Evaluation and Mitigation Strategy program to be able to prescribe, dispense, or receive rosiglitazone medicines.²⁰

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the thiazolidinediones.¹⁻⁶

There is insufficient evidence to support that one brand thiazolidinedione is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand thiazolidinedione is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Avandia® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2016 Sep.
2. Duetact® [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2015 Mar.
3. Actoplus Met® and Actoplus Met XR® [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2016 Dec.
4. Daily Med [database on the internet]. Bethesda (MD): National Library of Medicine; 2017 [cited 2017 Mar]. Available at: <http://dailymed.nlm.nih.gov/dailymed/about.cfm>.
5. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Mar]. Available from: <http://www.thomsonhc.com/>.
6. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Mar 2017]. Available from: <http://online.factsandcomparisons.com>.
7. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2016;39(Suppl. 1):S1–S112.
8. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.
9. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015 Mar;58(3):429-42.
10. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012 Feb 7;156(3):218-31.
11. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1:1-87.
12. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. Endocr Pract. 2016;22(1):84-113.
13. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management. [guideline on the Internet]. London: NICE; 2015 December [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng28>.
14. Redmon B, Caccamo D, Flavin P, Michels R, Myers C, O'Connor P, Roberts J, Setterlund L, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014.
15. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2012. [cited Oct 2014]. Available at www.idf.org.
16. Copeland, K.C., Silverstein, J., Moore, K.R., Prazar, G.E., Raymer, T., Shiffman, R.N., & et al. (2013). Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131(2):364-382.
17. National Institute for Health and Clinical Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng18>.
18. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management. [guideline on the Internet]. London: NICE; 2015 August [cited 2016 December]. Available from: <http://www.nice.org.uk/guidance/ng17>.
19. Chiang JL, Kirkman MS, Laffel LMB, and Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care 2014;37(7):2034-2054.
20. FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines [press release on the Internet]. Rockville (MD): Food and Drug Administration (US); 2013 Nov 25 [cited 2014 Nov 25]. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm>.
21. Dormandy JA, Charbonnel B, Eckland DJA, Erdmann E, Massi-Benedetti M, Moules IK, et al; on behalf of the PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the

- PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet*. 2005 Oct 8;366(9493):1279-89.
22. Erdmann E, Harding S, Lam H, Perez A. Ten-year observational follow-up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes. *Diabetes Obes Metab*. 2016 Mar;18(3):266-73.
 23. Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, et al; PROactive Investigators. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke*. 2007 Mar;38(3):865-73.
 24. Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM; PROactive Investigators. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol*. 2007 May 1;49(17):1772-80.
 25. Erdmann E, Charbonnel B, Wilcox RG, Skene AM, Massi-Benedetti M, Yates J, et al; on behalf of the PROactive Investigators. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive Study (PROactive 08). *Diabetes Care*. 2007 Nov;30(11):2773-8.
 26. Wilcox R, Kupfer S, Erdmann E. Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: results from PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive 10). *Am Heart J* 2008;155:712-7.
 27. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, Komajda M, et al; for the RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes-an interim analysis. *N Engl J Med*. 2007;357(1):28-38.
 28. Home P, Pocock S, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;373:2125-35.
 29. Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. *Am Heart J*. 2013;166(2):240-249.
 30. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA*. 2007 Sep 12;298(10):1180-8.
 31. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2006 Oct 18;(4):CD006060.
 32. Mannucci E, Monami M, Lamanna C, et al. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2008;10:1221-38.
 33. Nagajothi N, Adigopula S, Balamuthusamy S, et al. Pioglitazone and the risk of myocardial infarction and other major adverse cardiac events: a meta-analysis of randomized, controlled trials. *Am J Ther* 2008;15:506-11.
 34. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457-71.
 35. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA*. 2007 Sep 12;298(10):1189-95.
 36. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007 Jul 18;(3):CD006063.
 37. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. *Lancet*. 2007 Sep 29;370:1129-36.
 38. Karter AJ, Ahmed AT, Liu J, Moffet HH, Parker MM. Pioglitazone initiation and subsequent hospitalization for congestive heart failure. *Diabetic Med*. 2005 Aug;22:986-93.
 39. Gerrits CM, Bhattacharya M, Manthena S, Baran R, Perez A, Kupfer S. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. *Pharmacoepidemiol Drug Saf*. 2007 Oct;16(1):1065-71.
 40. Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA*. 2007 Dec 12;298(22):2634-43.
 41. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2005 Jul 20;(3):CD002966.
 42. Khan MA, St Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care*. 2002 Apr;25(4):708-11.

43. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, et al; for the GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care*. 2005 Jul;28(7):1547-54.
44. Tran MT, Navar MD, Davidson MB. Comparison of the glycemic effects of rosiglitazone and pioglitazone in triple oral therapy in type 2 diabetes. *Diabetes Care*. 2006;29(6):1395-6.
45. Derosa G, Cicero AFG, Gaddi A, Ragonesi PD, Fogari E, Bertone G, et al. Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with glimepiride: a twelve-month, multicenter, double-blind, randomized, controlled, parallel-group trial. *Clin Ther*. 2004;26(5):744-54.
46. Derosa G, D'Angelo A, Ragonesi PD, Ciccarelli L, Piccinni MN, Pricolo F, et al. Metformin-pioglitazone and metformin-rosiglitazone effects on nonconventional cardiovascular risk factors plasma level in type 2 diabetic patients with metabolic syndrome. *J Clin Pharm Ther*. 2006 Aug;31(4):375-83.
47. Berneis K, Rizzo M, Stettler C, et al. Comparative effects of rosiglitazone and pioglitazone on fasting and postprandial low-density lipoprotein size and subclasses in patients with Type 2 diabetes. *Expert Opin Pharmacother* 2008;9:343-9.
48. Chappuis B, Braun M, Stettler C, et al. Differential effect of pioglitazone (PGZ) and rosiglitazone (RGZ) on postprandial glucose and lipid metabolism in patients with type 2 diabetes mellitus: a prospective, randomized crossover study. *Diabetes Metab Res Rev* 2007;23:392-9.
49. Kikuchi M, Kaku K, Odawara M. Efficacy and tolerability of rosiglitazone and pioglitazone in drug-naïve Japanese patients with type 2 diabetes mellitus: a double-blind, 28 weeks' treatment, comparative study. *Curr Med Res Opin*; 2012: 28(6):1007-1016.
50. Pavo I, Jermendy G, Varkonyi TT, Kerényi Z, Gyimesi A, Shoustov S, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2003 Apr;88(4):1637-45.
51. Giles T, Miller A, Elkayam U, et al. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. *J Card Fail* 2008;14:445-52.
52. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al; for the ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Eng J Med*. 2006 Dec 7;355(23):2427-43.
53. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzolez JG, Chan M, et al. Efficacy and safety of exenatide once weekly vs metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4). *Diabetes Care*. 2012;35:252-8.
54. Nichols GA, Gomez-Caminero A. Weight changes following the initiation of new anti-hyperglycemic therapies. *Diabetes Obes Metab*. 2007 Jan;9(1):96-102.
55. Norris S, Carson S, Roberts C. Comparative effectiveness of pioglitazone and rosiglitazone in type 2 diabetes, prediabetes, and the metabolic syndrome: a meta-analysis. *Curr Diabetes Rev* 2007;3:127-40.
56. Singh S, Loke YK, Furberg CD. Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systemic review and meta-analysis. *Thorax*. 2011;66:383-8.
57. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta analysis. *CMAJ*. 2009;180(1):32-9.
58. Louisa M, Takeuchi M, Nafrialdi, Setiabudy R. A meta-analysis on treatment effects of thiazolidinediones for type 2 diabetes mellitus in Asian populations. *Acta Med Indones*. 2011 Jan;43(1):39-52.
59. Xu W, Bi Y, Sun Z, et al. Comparison of the effects on glycaemic control and β -cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE study). *J Intern Med*. 2015 Jan;277(1):137-50.
60. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med*. 2007 Sep 18;147(6):386-99.
61. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract*. 2008 Feb;79(2):196-203.
62. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD006423. DOI: 10.1002/14651858.CD006423.pub2.
63. Chogtu B, Singh N, Chawla S, et al. Impact of glitazones on metabolic and haemodynamic parameters in patients with type 2 diabetes mellitus. *Singapore Med J* 2009;50:395-9.
64. Brackenridge AL, Jackson N, Jefferson W, Stolinski M, Shojaee-Moradie F, Hovorka R, et al. Effects of rosiglitazone and pioglitazone on lipoprotein metabolism in patients with type 2 diabetes and normal lipids. *Diabet Med*. 2009;26:532-9.

65. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naïve patients with type 2 diabetes. *Diabetes Care*. 2010 Nov;33(11):2406-8.
66. DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2012 May;97(5):1615-22.
67. Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. *Diabetes Obes Metab*. 2011 Dec;13(12):1088-96.
68. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The Pioglitazone 027 Study Group. *Clin Ther*. 2000;22(12):1395-409.
69. Kaku K. Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial. *Curr Med Res Opin* 2009;25:1111-9.
70. Perez A, Zhao Z, Jacks R, et al. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. *Curr Med Res Opin* 2009;25:2915-2923.
71. Kipnes MS, Krosnick A, Rendell MS, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med*. 2001;111:10-7.
72. Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Schernthaner G. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. *Diabetes Metab Res Rev*. 2005;21(2):167-74.
73. Charbonnel B, Schernthaner G, Brunetti P, Matthews DR, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia*. 2005;48(6):1093-104. Epub 2005 May 12.
74. Hanefeld M, Brunetti P, Schernthaner GH, Matthews DR, Charbonnel BH; on behalf of the QUARTET Study Group. *Diabetes Care*. 2004 Jan;27(1):141-7.
75. Comaschi M, Corsi A, Di Pietro C, et al. The effect of pioglitazone as add-on therapy to metformin or sulphonylurea compared to a fixed-dose combination of metformin and glibenclamide on diabetic dyslipidaemia. *Nutr Metab Cardiovasc Dis* 2008;18:373-9.
76. Seufert J, Urquhart R. 2-year effects of pioglitazone add-on to sulfonylurea or metformin on oral glucose tolerance in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2008;79: 453-60.
77. Home PD, Shamanna P, Stewart M, et al. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. *Diabetes Obes Metab*. 2015 Feb;17(2):179-87.
78. Bergenstal RM, Wysham C, MacConell L, Malloy J, Walsh B, Yan P, et al. Efficacy and safety of exenatide once weekly vs sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomized trial. *Lancet*. 2010;376:431-9.
79. Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. *Am J Med*. 2004;15;116(4):230-5.
80. Dorkhan M, Frid A, Groop L. Differences in effects of insulin glargine or pioglitazone added to oral anti-diabetic therapy in patients with type 2 diabetes: what to add--insulin glargine or pioglitazone? *Diabetes Res Clin Pract* 2008;82:340-5.
81. Ligvay I, Legendre J, Kaloyanova P, et al. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? *Diabetes Care* 2009;32:1789-95.
82. Meneghini LF, Traylor L, Schwartz SL. Improved glycemic control with insulin glargine versus pioglitazone as add-on therapy to sulfonylurea or metformin in patients with uncontrolled type 2 diabetes mellitus (abstract). *Endocr Pract*. 2010 Jul-Aug;16(4):588-99.
83. Perez-Monteverde A, Seck T, Xu L, Lee MA, Sisk CM, Williams-Herman DE, et al. Efficacy and safety of sitagliptin and fixed-dose combination of sitagliptin and metformin vs pioglitazone in drug-naïve patients with type 2 diabetes. *Int J Clin Pract*. 2011 Sep;65(9):930-8.
84. Wainstein J, Katz L, Engel SS, Xu L, Golm GT, Hussain S, et al. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism*. 2012;14:409-18.

85. Takihata M, Nakamura A, Tajima K, et al. Comparative study of sitagliptin with pioglitazone in Japanese type 2 diabetic patients: the COMPASS randomized controlled trial. *Diabetes, Obesity and Metabolism* 2011;15(5):455-462.
86. Borges JLC, Bilezikian JP, Jones-Leone AR, Acosta AP, Ambery PD, Nino AJ, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naïve type 2 diabetes mellitus patients. *Diabetes, Obesity and Metabolism*. 2011;13:1036-46.
87. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. *JAMA*. 2000;283:1695-702.
88. Weissman P, Goldstein BJ, Rosenstock J, Waterhouse B, Cobitz AR, Wooddell MJ, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE study. *Curr Med Res Opin*. 2005 Dec;21(12):2029-35.
89. TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. 2012;366:2247-56.
90. Stewart MW, Cirkel DT, Furuseth K, Donaldson J, Biswas N, Starkie MG, et al. Effect of metformin plus rosiglitazone compared with metformin alone on glycemic control in well-controlled type 2 diabetes. *Diabet Med*. 2006 Oct;23:1069-78.
91. Rosak C, Petzoldt R, Wolf R, Reblin T, Dehmel B, Seidel D. Rosiglitazone plus metformin is effective and well tolerated in clinical practice: results from large observational studies in people with type 2 diabetes. *Int J Clin Pract*. 2005;59(10):1131-6.
92. Bailey CJ, Bagdonas A, Rubes J, McMorn SO, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. *Clin Ther*. 2005;27(10):1548-61.
93. Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. *Diabetes Obes Metab*. 2006;8:650-60.
94. Hamann A, Garcia-Puig J, Paul G, et al. Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with Type 2 diabetes inadequately controlled on metformin alone. *Exp Clin Endocrinol Diabetes* 2008;116:6-13.
95. Marre M, Shaw J, Brandle M, Bebakar WMW, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycemic and weight control compared to adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med*. 2009;26:268-78.
96. Rosenstock J, Rood J, Cobitz A, Huang C, Garber A. Improvement in glycaemic control with rosiglitazone/metformin fixed-dose combination therapy in patients with type 2 diabetes with very poor glycaemic control. *Diabetes Obes Metab*. 2006;8:643-9.
97. Fonseca V, Grunberger G, Gupta S, et al. Addition of nateglinide to rosiglitazone monotherapy suppresses mealtime hyperglycemia and improved overall glycemic control. *Diabetes Care*. 2003;26(6):1685-90.
98. Raskin P, Mill J, Saad MF, et al. Combination therapy for type 2 diabetes: repaglinide plus rosiglitazone. *Diabet Med*. 2004;21(4):329-35.
99. McCluskey D, Touger MS, Melis R, Schleusener DS, McCluskey D. Results of a randomized, double-blind, placebo-controlled study administering glimepiride to patients with type 2 diabetes mellitus inadequately controlled with rosiglitazone monotherapy. *Clin Ther*. 2004;26(11):1783-90.
100. Rosenstock J, Chou H, Matthaei S, et al. Potential benefits of early addition of rosiglitazone in combination with glimepiride in the treatment of type 2 diabetes. *Diabetes Obes Metab* 2008;10:862-73.
101. Chou H, Palmer J, Jones A, et al. Initial treatment with fixed-dose combination rosiglitazone/glimepiride in patients with previously untreated type 2 diabetes. *Diabetes Obes Metab* 2008;10:626-37.
102. Home PD, Jones NP, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, et al; for the RECORD Study Group. Rosiglitazone RECORD study: glucose control outcomes at 18 months. *Diabet Med*. 2007;24:626-34.
103. Komajda M, Curtis P, Hanefeld M, et al. Effect of the addition of rosiglitazone to metformin or sulfonylureas versus metformin/sulfonylurea combination therapy on ambulatory blood pressure in people with type 2 diabetes: a randomized controlled trial (the RECORD study). *Cardiovasc Diabetol*. 2008;7:10.
104. Scott R, Loeys T, Davies M, Engel S. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2008;10:959-969.

105. Rigby SP, Handelsman Y, Lai YL, et al. Effects of colesevelam, rosiglitazone, or sitagliptin on glycemic control and lipid profile in patients with type 2 diabetes mellitus inadequately controlled by metformin monotherapy. *Endocr Pract* 2010;16:53-63.
106. Hollander P, Li J, Allen E, Chen R. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. *J Clin Endocrinol Metab* 2009;94:4810-4819.
107. Pinelli NR, Cha R, Brown MB, Jaber LA. Addition of thiazolidinedione or exenatide to oral agents in type 2 diabetes: a meta-analysis. *Ann Pharmacother*. 2008;42(11): 1541-51.
108. Clar C, Royle P, Waugh N. Adding pioglitazone to insulin containing regimens in type 2 diabetes: systematic review and meta-analysis. *PLoS One* 2009;4:e6112.
109. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes Metab*. 2015 Mar;17(3):268-75.
110. Hollander P, Sugimoto D, Vlajnic A, Kilo C. Combination therapy with insulin glargine plus metformin but not insulin glargine plus sulfonylurea provides similar glycemic control to triple oral combination therapy in patients with type 2 diabetes uncontrolled with dual oral agent therapy. *J Diabetes Complications*. 2015 Nov-Dec;29(8):1266-71.
111. Scherthaner G, Rosas-Guzmán J, Dotta F, et al. Treatment escalation options for patients with type 2 diabetes after failure of exenatide twice daily or glimepiride added to metformin: results from the prospective European Exenatide (EUREXA) study. *Diabetes Obes Metab*. 2015 Jul;17(7):689-98.
112. Kheirbek RE, Alemi F, Zargoush M. Comparative effectiveness of hypoglycemic medications among veterans. *J Manag Care Pharm*. 2013;19(9):740-44.
113. Mearns ES, Sobieraj DM, White CM, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One*. 2015 Apr 28;10(4):e0125879.
114. Zinman B, Harris SB, Neuman J, Gerstein HC, Retnakaran RR, Raboud J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. *Lancet*. 2010;376:103-11.
115. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet*. 2006 Sep 23;368(9541):1096-105. Erratum in: *Lancet*. 2006 Nov 18;368(9549):1770.
116. Dagenais G, Gerstein H, Holman R, et al. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes Care* 2008;31:1007-14.
117. Vanderpoel DR, Hussein MA, Watson-Heidari T, Perry A. Adherence to a fixed-dose combination of rosiglitazone maleate/metformin hydrochloride in subjects with type 2 diabetes mellitus: a retrospective database analysis. *Clin Ther*. 2004;26(12):2066-75.
118. Berhanu P, Kipnes MS, Khan MA, Perez AT, Kupfer SF, Spanheimer RG, et al. Effects of pioglitazone on lipid and lipoprotein profiles in patients with type 2 diabetes and dyslipidemia after treatment conversion from rosiglitazone while continuing stable statin therapy. *Diab Vasc Dis Res*. 2006 May;3(1):39-44.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antidiabetic Agents, Miscellaneous
AHFS Class 682092
May 10, 2017**

I. Overview

Mifepristone (Korlym[®]) is classified as an antidiabetic agent, miscellaneous by the American Hospital Formulary Service. Mifepristone is a cortisol receptor blocker Food and Drug Administration (FDA)-approved to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance and have failed surgery or are not candidates for surgery.^{1,2} Mifepristone is the first and only approved medication for Cushing's syndrome patients and has been designated as an Orphan Drug by the FDA for this indication.³ When administered in high doses, mifepristone is a selective antagonist of the GR-II glucocorticoid receptor and blocks the effects of cortisol. Mifepristone and the three active metabolites have a greater affinity for the glucocorticoid receptor compared to dexamethasone and cortisol, and have little to no affinity for estrogen, muscarinic, histaminic, or monoamine receptors. Of note, mifepristone does not reduce cortisol levels.^{1,4}

Excess cortisol production, the biochemical hallmark of endogenous Cushing's syndrome, may be caused by either excess adrenocorticotrophic hormone secretion (from a pituitary or other ectopic tumor) or independent adrenal overproduction of cortisol. Clinical features of Cushing's syndrome typically reflect prolonged and inappropriately high exposure to glucocorticoids, including weight gain, severe fatigue and muscle weakness, high blood pressure, depression, cognitive impairment, purplish skin striae, easy bruising, loss of libido, diabetes, hirsutism, acne, and mental disorders.⁵⁻⁶ Medical therapies may have a primary or adjunctive role in some patients. In patients in whom surgery has failed to control the disease, medical management is essential to reduce or normalize hypercortisolemia, and should be utilized prior to considering bilateral adrenalectomy. Medical therapies consist of adrenolytic agents (ketoconazole, metyrapone, aminoglutethimide [not available in the United States], mitotane, and etomidate) and neuromodulatory agents (somatostatin analogs, dopamine agonists, peroxisome proliferator-activated receptor- γ agonists, retinoic acid, and glucocorticoid receptor antagonists).⁵⁻⁷ Adrenolytic agents typically work to decrease cortisol levels and are the most widely used agents. In particular, among patients with hypercortisolism in whom medical therapy is indicated, ketoconazole is considered first-line therapy.⁷ The safety and efficacy of neuromodulatory therapies in endogenous Cushing's syndrome are still being evaluated.⁶

At lower doses mifepristone is a selective antagonist of the progesterone receptor.¹ The agent is also available as the branded agent Mifeprex[®], which is FDA-approved for the medical termination of intrauterine pregnancy through 49 days of pregnancy.⁸

The antidiabetic agents, miscellaneous that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Currently Mifepristone (Korlym[®]) is the only agent in the class and although the class has been reviewed previously this is the first review of Mifepristone (Korlym[®]). This class was last reviewed in February 2015.

Table 1. Antidiabetic Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Mifepristone	tablet	Korlym [®]	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

No clinical guidelines regarding the treatment of Cushing's syndrome were identified.

III. Indications

The Food and Drug Administration (FDA)-approved indication for mifepristone is noted in Table 2.

Table 2. FDA-Approved Indications for the Antidiabetic Agents, Miscellaneous¹⁻²

Indication	Mifepristone
Control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed or who are not candidates for surgery	✓

IV. Pharmacokinetics

The pharmacokinetic parameters of the antidiabetic agents, miscellaneous are listed in Table 3.

Table 3. Pharmacokinetic Parameters of the Antidiabetic Agents, Miscellaneous^{1,3}

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Half-Life (hours)
Mifepristone	69	96.1 to 99.2	Liver (extensive, % not reported)	20 to 85

V. Drug Interactions

Significant drug interactions with the antidiabetic agents, miscellaneous are listed in Table 4. Due to the long serum half-life of mifepristone, at least two weeks should elapse after cessation of mifepristone before initiating or increasing the dose of any interacting concomitant medication.¹

Discontinuation or dose reduction of drugs whose metabolism is largely or solely mediated by cytochrome P450 (CYP) 3A may be necessary with mifepristone coadministration. Other drugs with similar high first pass metabolism in which CYP3A is the primary route of metabolism should be used with extreme caution if co-administered with mifepristone.¹ Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of mifepristone may be required. Avoid coadministration of mifepristone and CYP3A inducers.¹

Mifepristone is a progesterone-receptor antagonist and will interfere with the effectiveness of hormonal contraceptives; therefore, non-hormonal contraceptive methods should be used.¹

Table 4. Significant Drug Interactions with the Antidiabetic Agents, Miscellaneous²

Generic Name(s)	Interaction	Mechanism
Mifepristone	CYP2C8/2C9 metabolized drugs (e.g., fluvastatin, NSAIDs, warfarin, repaglinide)	Because mifepristone is an inhibitor of CYP2C8/2C9, concurrent use of mifepristone with a drug whose metabolism is largely or solely mediated by CYP2C8/2C9 is likely to result in increased plasma concentrations of the drug.
Mifepristone	CYP2B6 metabolized drugs (e.g., bupropion, efavirenz)	Mifepristone is an inhibitor of CYP2B6 and may cause significant increases in exposure of drugs that are metabolized by CYP2B6. Since no study has been conducted to evaluate the effect of mifepristone on substrates of CYP2B6, the concomitant use of bupropion and efavirenz should be undertaken with caution.

VI. Adverse Drug Events

The most common adverse drug events reported with the antidiabetic agents, miscellaneous are listed in Table 5. The boxed warning for mifepristone is listed in Table 6.

Table 5. Adverse Drug Events (%) Reported with Antidiabetic Agents, Miscellaneous¹⁻²

Adverse Event	Mifepristone
Gastrointestinal	
Constipation	10
Diarrhea	12
Dry mouth	18
Nausea	48
Vomiting	26
General Disorders and Administration/Site Conditions	
Edema peripheral	26
Fatigue	48
Pain	14
Infections and Infestations	
Nasopharyngitis	12
Sinusitis	14
Investigations	
Blood potassium decreased	34
Thyroid function test abnormal	18
Metabolism and Nutrition Disorders	
Anorexia	10
Decreased appetite	20
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	30
Back pain	16
Myalgia	14
Pain in extremity	12
Nervous System	
Dizziness	22
Headache	44
Somnolence	10
Psychiatric Disorders	
Anxiety	10
Reproductive System and Breast Disorders	
Endometrial hypertrophy	38*
Respiratory, Thoracic, and Mediastinal Disorders	
Dyspnea	16
Vascular Disorders	
Hypertension	24

*The denominator was 26 females who had baseline and end-of-trial transvaginal ultrasound.

✓ Percent not specified.

Table 6. Boxed Warning for Korlym® (mifepristone)¹

WARNING
<p>Mifepristone is a potent antagonist of progesterone and cortisol via the progesterone and glucocorticoid (GR-II) receptors, respectively. The antiprogesterational effects will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with mifepristone and prevented during treatment and for one month after stopping treatment by the use of a non-hormonal medically acceptable method of contraception unless the patient has had a surgical sterilization, in which case no additional contraception is needed. Pregnancy must also be excluded if treatment is interrupted for more than 14 days in females of reproductive potential.</p>

VII. Dosing and Administration

The usual dosing regimen for the antidiabetic agents, miscellaneous are listed in Table 7.

Table 7. Usual Dosing Regimens for Antidiabetic Agents, Miscellaneous¹⁻²

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Mifepristone	<u>Control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery:</u> Tablet: initial, 300 mg once daily as a single dose with a meal; maximum, 1,200 mg QD or 20 mg/kg/day	Safety and efficacy in pediatric patients have not been established.	Tablet: 300 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antidiabetic agents, miscellaneous are summarized in Table 8.

Table 8. Comparative Clinical Trials with Antidiabetic Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Fleseriu et al.⁹ (2012)</p> <p>Mifepristone 300 to 1,200 mg QD</p> <p>Patients started with 300 mg QD and if no significant clinical improvement, doses could be increased to 600 mg QD on day 14, 900 mg QD at week 6 and 1,200 mg QD at week 10.</p>	<p>MC, OL</p> <p>Adults with confirmed endogenous CS with type 2 diabetes mellitus, impaired glucose tolerance, or a diagnosis of hypertension in addition to ≥ 2 of the following symptoms: Cushingoid appearance (moon facies, dorsocervical fat pad, and plethora), increased body weight or central obesity, proximal muscle weakness, low bone mineral density (T score < -1.0), psychiatric symptoms, and skin changes (hirsutism, violaceous striae, or acne)</p>	<p>N=50</p> <p>24 weeks</p>	<p>Primary: Change $\geq 25\%$ in AUC_{glucose} on oGTT from baseline (for patients with CS and type 2 diabetes mellitus or impaired glucose tolerance [C-DM cohort]) and change ≥ 5 mm Hg in DBP from baseline to week 24 (for patients with hypertension [C-HT cohort])</p> <p>Secondary: Changes in glucose homeostasis, BP, lipids, weight, body composition change, clinical appearance, strength, neuropsychological and quality of life parameters and safety</p>	<p>Primary: In the C-DM mITT population, the AUC_{glucose} was reduced by $\geq 25\%$ on oGTT in 60% (15/25) of patients receiving mifepristone compared to baseline ($P < 0.001$).</p> <p>In the C-HT mITT treatment group, 38.1% (8/21) of patients treated with mifepristone achieved ≥ 5 mm Hg decline in DBP compared to baseline ($P < 0.05$).</p> <p>Secondary: Overall, the clinical responder rate was 87% at week 24 compared to baseline ($P < 0.0001$). Specifically, 92% of patients in the C-DM group and 81% of those in the C-HT group achieved a median clinical improvement score of +1 (P values not reported).</p> <p>Overall, FPG decreased from 149.0 ± 74.7 mg/dL at baseline to 104.7 ± 37.5 mg/dL after 24 weeks ($P < 0.03$). In the C-DM group, 72% of patients achieved $\geq 25\%$ reduction from baseline in AUC_{glucose} or a reduction in antidiabetic medication (95% CI, 50.6 to 87.9). The mean HbA_{1c} was significantly reduced from baseline following mifepristone treatment (6.29 ± 0.99 vs $7.43 \pm 1.52\%$; $P < 0.001$). Of the 12 patients with an $HbA_{1c} > 7.0\%$ at baseline, nine were able to lower their HbA_{1c} below 7.0%, including six reaching an HbA_{1c} 6.0% or below. Patients in both the C-DM and C-HT treatment groups who were insulin resistant at baseline demonstrated rapid and significant improvements in AUC_{insulin}, which continued throughout the study. Insulin sensitivity was improved as evident by changes in HOMA-IR.</p> <p>In the mITT group, the mean \pm SD change in bodyweight from baseline to week 24 following mifepristone treatment was $-5.7 \pm 7.4\%$ ($P < 0.001$). Overall, 24 mifepristone-treated patients lost $\geq 5\%$ of their baseline weight, and 10 patients lost $\geq 10\%$.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Mifepristone treatment was associated with a statistically significant reduction in waist circumference in women (-6.8±5.8 cm; P<0.001) and men (-8.4±5.9 cm; P<0.001).</p> <p>At week 24, the mean total body fat declined by 3.6% (P<0.001), absolute fat mass declined by 13.9% (P<0.001), total body of the trunk declined by 15.6% (P<0.001) and by 17.1% (P<0.001) for the abdominal region.</p> <p>Overall, 52.5% of patients with hypertension at baseline had either a response in DBP or a reduction in antihypertensive medication use. There were no statistically significant differences in mean SBP and DBP from baseline after 24 weeks of treatment in C-HT patients (129.5±16.3/82.9±11.4 vs 129.9±19.0/82.8±13.2 mm Hg) or in C-DM patients who also had hypertension (137.7±24.0/86.4±15.3 vs 132.2±16.7/82.4±13.2 mm Hg).</p> <p>There were statistically significant improvements in the median BDI-II depression scores in the mITT population (P<0.001). For patients with at least mild depression at baseline, (BDI-II >14), the median score improved from 23 to 12 at 24 weeks (P<0.001). Similarly, improvements in cognition scores were also reported (P<0.01). Patients treated with mifepristone experienced statistically significant improvements in quality of life scores at 24 weeks compared to baseline in both mental (P=0.01) and physical (P=0.02) composite scores.</p> <p>Adverse events occurred in 88% of mifepristone-treated patients, with the most common being nausea (48%), fatigue (48%), headache (44%), decreased blood potassium (34%), arthralgia (30%), vomiting (26%), peripheral edema (26%), hypertension (24%), dizziness (22%), decreased appetite (20%), and endometrial thickening (20%). Seven patients discontinued mifepristone due to adverse events.</p>

Drug regimen abbreviations: QD=once daily

Study abbreviations: CI=confidence interval, MC=multicenter, OL=open label

Miscellaneous abbreviation: AUC_{glucose}=area under the curve for glucose, AUC_{insulin}= area under the curve for insulin, BDI-II-Beck depression inventory, BP=blood pressure, CS=Cushing's syndrome, DBP=diastolic blood pressure, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin A_{1c}, HOMA-IR=homeostatic model assessment of insulin resistance, mITT=modified intent to treat, oGTT=oral glucose tolerance test, QOL=quality of life, SBP=systolic blood pressure, SD=standard deviation

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 8. Relative Cost of Antidiabetic Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Mifepristone	tablet	Korlym®	\$\$\$\$\$	N/A

N/A=Not available

X. Conclusions

Mifepristone is the first agent Food and Drug Administration (FDA)-approved for the management of Cushing’s syndrome.¹⁻³ Specifically, mifepristone is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing’s syndrome who have type 2 diabetes or glucose intolerance and have failed surgery or are not candidates for surgery. Mifepristone should not be used for the treatment of type 2 diabetes unrelated to endogenous Cushing’s syndrome.¹ Mifepristone has been designated as an Orphan Drug for the treatment of the clinical manifestations of endogenous Cushing’s syndrome by the FDA.³

There is an overall lack of guidance within published literature and clinical guidelines as to the role of mifepristone in the management of endogenous Cushing’s syndrome. Following 24 weeks of treatment with mifepristone in patients with Cushing’s syndrome, there were reductions in glucose area under the curve and reductions in diastolic blood pressure in adult patients with type 2 diabetes, glucose tolerance or hypertension.⁸ Patients receiving mifepristone have also demonstrated varying degrees of improvement in Cushing’s syndrome manifestations; however, it is not clear as to whether these changes are a result of mifepristone treatment.⁸

Based on the mechanism of action of mifepristone and its approved indication, the agent can only be used in certain patients with endogenous Cushing’s syndrome and there is potential for it to be used in combination with

other established treatments. Cushing's syndrome treatment goals include the reversal of clinical features, the normalization of biochemical changes with minimal morbidity, and long-term control without recurrence. Optimal treatment is surgical resection by selective adenomectomy, with second-line options that include repeated pituitary surgery, radiotherapy, or bilateral adrenalectomy.⁶ Medical therapy plays an essential role in patients in whom surgery has failed to control the disease to reduce or normalize hypercortisolemia. Currently, adrenolytic therapies (ketoconazole, metyrapone, aminoglutethimide [not available in the United States], mitotane, etomidate) are the most widely utilized agents, with fluconazole considered first-line to treat hypercortisolism. The safety and efficacy of neuromodulatory therapies (somatostatin analogs, dopamine agonists, peroxisome proliferator-activated receptor- γ agonists, retinoic acid, glucocorticoid receptor antagonists) in Cushing's syndrome have not been established.⁵⁻⁶

There is insufficient evidence to support that one brand antidiabetic agent, miscellaneous is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand antidiabetic agent, miscellaneous is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Korlym[®] [package insert]. Menlo Park (CA): Corcept Therapeutics Incorporated; 2016 Oct.
2. Facts and Comparisons[®] eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Mar 2017]. Available from: <http://online.factsandcomparisons.com>.
3. Corcept Therapeutics Incorporated announces FDA approval of Korlym[®] (mifepristone) 300 mg tablets: first and only approved medication for Cushing's syndrome patients [press release on the Internet]. Menlo Park (CA): Corcept Therapeutics Incorporated; 2012 Feb [cited 2012 Sept]. Available from: <https://www.korlym.com/>.
4. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Mar]. Available from: <http://www.thomsonhc.com/>.
5. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008 May;93(5):1526-40.
6. Mancini T, Porcelli T, Giustina A. Treatment of Cushing disease: overview and recent findings. *Ther Clin Risk Manag*. 2010 Oct 21;6:505-16.
7. Nieman K. Medical therapy of hypercortisolism (Cushing's syndrome). In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2017 [cited 2017 Mar]. Available from: <http://www.utdol.com/utd/index.do>.
8. Mifeprex[®] [package insert]. New York (NY): Danco Laboratories; 2016 Mar.
9. Fleseriu M, Biller BM, Findling JW, Molitch ME, Scheingart DE, Gross C, et al. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *J Clin Endocrinol Metab*. 2012 Jun;97(6):2039-49.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Multivitamin Preparations: Prenatal Vitamins
AHFS Class 882800
May 10, 2017**

I. Overview

Women of reproductive age should maintain good nutritional status prior to, during, and after pregnancy to minimize health risks to both the mother and child. This includes maintaining a healthy weight, participating in physical activity, consuming a variety of foods to meet the Dietary Reference Intake recommendations, as well as appropriate and timely supplementation with multivitamins.¹⁻³ There are several organizations that have published dietary guidelines for the perinatal period (preconception, pregnancy, and during lactation).⁴⁻⁶ However, most women of childbearing age do not maintain a healthy diet and do not consume enough vitamins (A, C, B-6, and E), calcium, folic acid, iron, magnesium, or zinc.^{1,2}

Women have an increased requirement for certain nutrients during pregnancy, including folate and iron. Folate is necessary for deoxyribonucleic acid (DNA) synthesis and cell division and is an important nutrient prior to and during pregnancy. Many studies have shown that folic acid supplementation is associated with a lower risk of neural tube defects, which are serious birth defects of the spine and brain.¹⁻¹¹ The American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), American College of Obstetricians and Gynecologists (ACOG), American Dietetic Association (ADA), Centers for Disease Control and Prevention (CDC), and the United States Preventive Services Task Force (USPSTF) all recommend that women of reproductive age consume folic acid on a daily basis.^{1,7-11} The amount of folic acid that is recommended varies slightly among the organizations; however, the most recent publication by the USPSTF recommends that all women planning pregnancy take a supplement containing 400 to 800 µg of folic acid on a daily basis.⁸ A higher dose of folic acid (4 mg/day) is recommended for women who have had a previous pregnancy affected by a neural tube defect, which should begin one to three months prior to conception and continue throughout the first trimester of pregnancy.^{2,8-9,11}

Iron deficiency is common in women of childbearing age due to menstruation, insufficient dietary intake, and multiple pregnancies.² There is an increase in iron requirements during pregnancy due to the expansion of blood volume and red blood cell mass.¹² Iron deficiency anemia during pregnancy can lead to fetal complications such as premature delivery, intrauterine growth restrictions, and neonatal mortality.^{2,12} It is recommended that women consume 27 mg of elemental iron per day during pregnancy.⁵ Pregnant women should be screened for iron deficiency anemia, and if present, be treated with supplemental iron (60 to 120 mg/day).^{1-3,12}

There is evidence that maternal consumption of folic acid-containing multivitamins may reduce the risk of neural tube defects, cardiac defects, urinary tract defects, limb defects, as well as other birth defects.^{2,13} The ADA recommends supplementation with a multivitamin for pregnant women with iron deficiency anemia, poor-quality diets, those who consume no or small amounts of animal source foods, women carrying two or more fetuses, those who smoke or abuse alcohol or drugs, and for women who are infected with human immunodeficiency virus.¹ In addition to a well-balanced diet, supplementation with a folic acid-containing multivitamin should be encouraged in all women of reproductive age to help support healthy pregnancy outcomes.²

There is a wide variety of prenatal vitamins currently available. Most of the preparations contain folic acid and iron; however, the amount varies among the products (refer to the dosing and administration section for comparison). The products also contain various combinations and quantities of vitamins and minerals. Additional nutrients which may be added to a prenatal vitamin include aspartame, docusate, L-methylfolate, omega-3 fatty acids, and omega-6 fatty acids. Folic acid must be broken down to L-methylfolate to be used at the cellular level; however, some individuals are unable to convert folic acid to its active form. Some of the prenatal formulations contain L-methylfolate for women who are unable to fully metabolize folic acid. Omega-3 fatty acids include α -linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). Omega-3 and omega-6 fatty acids must be obtained from food because the human body cannot synthesize these nutrients. DHA and EPA can be synthesized de novo from ALA; however, intake of ALA has not been shown to increase maternal, fetal, or breast milk DHA levels.²⁻³ Both DHA and EPA are considered essential fatty acids which are necessary for

nervous tissue growth and function.¹⁴ Some studies suggest that they may play a role in fetal/neonatal visual and neural growth when taken during pregnancy, as well as help prevent low birth weight. There are recommended DRIs that have been established for ALA; however, it is unclear how much DHA or EPA a pregnant woman should consume through her diet and via supplementation.^{2-3,15}

The prenatal vitamins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. It should be noted that the products included in this review contain an extensive ingredient list, which can be found separately in the prescribing information. The term “prenatal vitamins” in Table 1 collectively refers to all of the active vitamin and mineral ingredients. Additional ingredients, including folic acid and iron, have been listed out separately. Many of the prenatal vitamins are available in a generic formulation, including products which contain omega-3 fatty acids. This class was last reviewed in February 2015.

Table 1. Prenatal Vitamins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Iron, folic acid, multivitamins with minerals	Tablet	OB Complete [®]	none
Prenatal vitamins, folic acid	Chewable tablet	Prenate [®]	none
Prenatal vitamins, folic acid, ginger oil	Tablet	Prenate AM [®]	none
Prenatal vitamins, iron, folic acid	Capsule, chewable tablet, tablet	Concept OB ^{®*} , Nestabs ^{®*} , Niva-Plus ^{®*} , OB-Complete Premier [®] , Prefera OB ^{®*} , Prenata [®] , Prenate Elite [®] , Prenate Star [®] , Provida OB [®] , Select-OB [®] , Thrivite Rx ^{®*} , Tricare [®] , Vinate II [®] , Vinate Care [®] , Vitafol Nano [®] , Vitafol-OB [®]	prenatal vitamins, iron, folic acid
Prenatal vitamins, iron, folic acid, DHA	Capsule, chewable tablet, combination package	Active OB [®] , Enbrace HR [®] , Natelle One ^{®*} , Nestabs DHA ^{®*} , OB Complete Petite [®] , OB Complete Gold [®] , Prefera-OB One [®] , Prefera-OB Plus DHA [®] , Prenate DHA [®] , Prenate Enhance [®] , Prenate Essential [®] , Prenate Mini [®] , Prenate Pixie [®] , Prenate Restore [®] , Primacare [®] , Provida DHA [®] , Select-OB+DHA [®] , Tristart DHA [®] , Vitafol-OB+DHA [®] , Vitafol-One [®] , Vitafol Ultra [®]	prenatal vitamins, iron, folic acid, DHA
Prenatal vitamins, iron, folic acid, docusate	Tablet	Citranatal RX [®]	prenatal vitamins, iron, folic acid, docusate
Prenatal vitamins, iron, folic acid, omega-3 fatty acids	Capsule, combination package	Bal-Care DHA Essential ^{®†} , Concept DHA ^{®*} , OB Complete With DHA [®] , PR Natal 400 ^{®*} , PR Natal 430 [®] , PR Natal 400 EC [®] , PR Natal 430 EC [®] , Relnate ^{®*}	prenatal vitamins, iron, folic acid, omega-3 fatty acids
Prenatal vitamins, iron, folic acid, selenium	Tablet	Vinate-M ^{®*}	prenatal vitamins, iron, folic acid, selenium
Prenatal vitamins, iron, folic acid, vitamin B6	Tablet	Citranatal B-Calm [®]	prenatal vitamins, iron, folic acid, vitamin B6
Prenatal vitamins, iron, folic	Capsule, combination	Citranatal 90 DHA ^{®*} ,	prenatal vitamins, iron,

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
acid, DHA, docusate	package	Citranatal Assure ^{®*} , Citranatal DHA [®] , Citranatal Harmony [®] , Nexa Plus [®] , Vitafol Fe + Docusate [®]	folic acid, DHA, docusate
Prenatal vitamins, iron, folic acid, DHA, EPA	Combination package	Nestabs ABC [®]	none
Prenatal vitamins, iron, folic acid, DHA, fish oil	Capsule	OB Complete One [®]	none
Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids	Combination package	Prenatal Plus-DHA [®]	none
Prenatal vitamins, iron, folic acid, docusate, omega-3 fatty acids	Capsule	N/A	prenatal vitamins, iron, folic acid, docusate, omega-3 fatty acids
Prenatal vitamins, iron, folic acid, DHA, docusate, ubidecarenone	Tablet	Preque 10 [®]	none
Prenatal vitamins, iron, folic acid, DHA, docusate, EPA, fish oil	Capsule	Tricare Prenatal DHA One ^{®*}	prenatal vitamins, iron, folic acid, DHA, docusate, EPA, fish oil
Prenatal vitamins, iron, folic acid, DHA, EPA, omega-3 fatty acids	Chewable tablet	Vitafol Gummies [®]	none
Prenatal vitamins, iron, L-methylfolate	Chewable tablet	Tricare Prenatal Chewable [®]	none
Prenatal vitamins, iron, L-methylfolate, algal oil blend, soy [†]	Capsule	Vinate DHA RF ^{®†}	none
Prenatal vitamins, iron, L-methylfolate, DHA, EPA, omega-3 fatty acids	Combination package	Tricare Prenatal with DHA [®]	none

*Generic is available in at least one dosage form or strength.

†Clinical information for this product is not available in the various drug databases.

DHA=Docosahexaenoic acid

EPA=Eicosapentaenoic acid

N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the prenatal vitamins are summarized in Table 2. The recommended Dietary Reference Intakes for women are listed in Table 3.

Table 2. Treatment Guidelines Using the Prenatal Vitamins

Clinical Guideline	Recommendation(s)
United States Preventive Services Task Force: Folic Acid for the Prevention of Neural Tube Defects: United States Preventive Services Task Force Recommendation Statement (2009)⁸	<ul style="list-style-type: none"> All women planning or capable of pregnancy should take a daily supplement containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid. This recommendation applies to women who are planning or capable of pregnancy, but it does not apply to women who have had a previous pregnancy affected by neural tube defects or women taking certain antiseizure medicines. Most organizations recommend that these women take higher doses of folic acid. Most studies indicate the need to start folic acid supplementation at least one month before conception and to continue daily supplements through the first two to three months of pregnancy. Studies also indicate that 50% of pregnancies in the United States are unplanned, and clinicians should therefore

Clinical Guideline	Recommendation(s)
	<p>advise all women who are capable of pregnancy to take folic acid supplements.</p> <ul style="list-style-type: none"> • Good evidence from randomized trials in settings without fortification of food suggests that a multivitamin with 0.8 mg (800 µg) of folic acid reduces the risk for neural tube defects. Observational studies done before fortification report a reduction of neural tube defects in women taking a supplement with 0.4 mg (400 µg) of folic acid (the generally available dose). Evidence indicates that most women in the United States are not ingesting fortified foods at a level thought to provide optimal benefit. In a setting in which food is fortified with folic acid, the effective amount of additional folic acid supplementation is unclear.
<p>Position of the American Dietetic Association: Nutrition and Lifestyle for a Healthy Pregnancy Outcome (2014)¹</p>	<ul style="list-style-type: none"> • Women of childbearing age should adopt a lifestyle optimizing health and reducing risk of birth defects, suboptimal fetal development, and chronic health problems in both mother and child. Components leading to healthy pregnancy outcome include healthy prepregnancy weight, appropriate weight gain and physical activity during pregnancy, consumption of a wide variety of foods, appropriate vitamin and mineral supplementation, avoidance of alcohol and other harmful substances, and safe food handling. • During the first two trimesters of pregnancy, iron-deficiency anemia increases the risk for preterm labor, low birth weight, and infant mortality. Maternal and fetal demand for iron increases during pregnancy; this increase cannot be met without iron supplementation. • All women, including adolescents, who are capable of becoming pregnant should consume 400 µg/day folic acid from fortified foods and/or dietary supplements, in addition to eating food sources of folate. Pregnant women are advised to consume 600 µg dietary folate equivalents daily from all food sources. Folic acid is recognized as important before and during pregnancy because of its preventive properties against neural tube defects. Women who have had an infant with a neural tube defect should consult with their health care provider regarding the recommendation to take 4,000 µg folic acid daily before and throughout the first trimester of pregnancy. • Vitamin D supplementation during pregnancy has been suggested as an intervention to protect against adverse outcomes, including low birth weight; however, the need, safety, and effectiveness of vitamin D supplementation remains controversial. The Institute of Medicine recommends 600 IU per day of vitamin D, and ongoing research suggests higher levels are safe and effective for improving maternal and infant vitamin D status. • Although choline is found in many foods, the majority of pregnant women are not achieving the adequate intake for pregnancy of 450 mg/day. Recommended calcium intake is equal for pregnant and nonpregnant women of the same age. Women with suboptimal intakes (<500 mg/day) may need additional amounts to meet maternal and fetal bone requirements. The recommended amount of iodine from dietary and supplement sources is 150 µg/day before conception and 220 µg/day for pregnant women.
<p>The American College of Obstetricians and Gynecologists Practice Bulletin: Anemia in Pregnancy (2008)¹² (Reaffirmed 2015)</p>	<ul style="list-style-type: none"> • All pregnant women should be screened for anemia during pregnancy. Those with iron deficiency anemia should be treated with supplemental iron, in addition to prenatal vitamins. Patients with anemia other than iron deficiency anemia should be further evaluated. • Iron deficiency anemia during pregnancy has been associated with an increased risk of low birth weight, preterm delivery, and perinatal mortality. • Severe anemia with maternal hemoglobin levels <6 grams/dL has been associated with abnormal fetal oxygenation resulting in nonreassuring fetal heart rate patterns, reduced amniotic fluid volume, fetal cerebral vasodilatation, and fetal death. Thus, maternal transfusion should be considered for fetal indications. • Iron supplementation decreases the prevalence of maternal anemia at delivery. However, it is unclear whether iron supplementation in well-nourished

Clinical Guideline	Recommendation(s)
	<p>pregnant women who are not anemic affects perinatal outcomes.</p> <ul style="list-style-type: none"> • There is little evidence that iron supplementation results in morbidity beyond gastrointestinal symptoms, except in patients with hemochromatosis or certain other genetic disorders.
<p>American Academy of Family Physicians: Clinical Preventative Service Recommendation: Neural Tube Defects (2009)¹¹</p>	<ul style="list-style-type: none"> • It is recommended that all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid.
<p>Centers for Disease Control and Prevention: Recommendations to Improve Preconception Health and Health Care-United States (2006)⁷</p>	<p><u>Preconception risk factors for adverse pregnancy outcomes</u></p> <ul style="list-style-type: none"> • Alcohol misuse <ul style="list-style-type: none"> ○ It is not safe to drink alcohol at any time during pregnancy, and harm can occur early, before a woman realizes that she is or might be pregnant. Fetal alcohol syndrome and other alcohol-related birth defects can be prevented if women stop drinking alcohol before conception. • Anti-epileptic drugs <ul style="list-style-type: none"> ○ Certain anti-epileptic drugs (e.g., valproic acid) are known teratogens. Recommendations suggest that women who are on a regimen of these drugs and who are contemplating pregnancy should be prescribed a lower dosage of these drugs. • Diabetes (preconception) <ul style="list-style-type: none"> ○ The threefold increase in the prevalence of birth defects among infants of women with type 1 and type 2 diabetes is substantially reduced through proper management of diabetes. • Folic acid <ul style="list-style-type: none"> ○ Daily use of vitamin supplements containing folic acid has been shown to reduce the occurrence of neural tube defects by as much as two thirds. • Hepatitis B <ul style="list-style-type: none"> ○ Vaccination is recommended for men and women who are at risk for acquiring hepatitis B virus (HBV) infection. Preventing HBV infection in women of childbearing age prevents transmission of infection to infants and eliminates risks to the women of HBV infection and sequelae, including hepatic failure, liver carcinoma, cirrhosis, and death. • HIV/acquired immune deficiency syndrome <ul style="list-style-type: none"> ○ If HIV infection is identified before conception, timely antiretroviral treatment can be administered, and women (or couples) can be given additional information to help prevent mother-to-child transmission. • Hypothyroidism <ul style="list-style-type: none"> ○ The dosages of thyroxine (e.g., levothyroxine) need to be adjusted for proper neurologic development of the fetus. • Isotretinoin <ul style="list-style-type: none"> ○ Use of isotretinoin (e.g., Accutane[®]) to treat acne during pregnancy can result in miscarriage and birth defects. Effective pregnancy prevention should be implemented to avoid unintended pregnancies among women with childbearing potential who use this medication. • Maternal phenylketonuria <ul style="list-style-type: none"> ○ Women diagnosed with maternal phenylketonuria as infants have an increased risk for delivering infants with mental retardation or birth defects. However, this adverse outcome can be prevented when mothers adhere to a low-phenylalanine diet before conception and continue it throughout their pregnancy.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Rubella seronegativity <ul style="list-style-type: none"> ○ Rubella vaccination provides protective seropositivity and prevents congenital rubella syndrome. • Obesity <ul style="list-style-type: none"> ○ Adverse perinatal outcomes associated with maternal obesity include neural tube defects, preterm delivery, diabetes, cesarean delivery, and hypertensive and thromboembolic disease. Appropriate weight loss and nutritional intake before pregnancy reduces these risks.
<p>The American College of Obstetricians and Gynecologists Practice Bulletin: Neural Tube Defects (2003)⁹ (Reaffirmed 2014)</p>	<ul style="list-style-type: none"> • Periconceptional folic acid supplementation is recommended because it has been shown to reduce the occurrence and recurrence of neural tube defects. • For low-risk women, folic acid supplementation of 400 µg per day currently is recommended because nutritional sources alone are insufficient. Higher levels of supplementation should not be achieved by taking excess multivitamins because of the risk of vitamin A toxicity. • The ideal dose for folic acid supplementation has not been appropriately evaluated in prospective clinical studies. A 400 µg supplement currently is recommended for women capable of becoming pregnant. • For women at high risk of neural tube defects or who have had a previous pregnancy with a neural tube defect, folic acid supplementation of 4 mg per day is recommended.
<p>American Academy of Pediatrics: Folic Acid for the Prevention of Neural Tube Defects (1999)¹⁰ (Reaffirmed May 2012)</p>	<ul style="list-style-type: none"> • The American Academy of Pediatrics (AAP) endorses the United States Preventive Services Task Force recommendation that all women of childbearing age who are capable of becoming pregnant should consume 400 (0.4 mg) µg of folic acid daily. • Women with a history of a previous pregnancy resulting in a fetus with neural tube defects should be advised of the results of the Medical Research Council Vitamin (MRC) study. During times in which a pregnancy is not planned, these high-risk women should consume 4000 (4 mg) µg of folic acid per day. However, they should be offered treatment with 4000 µg of folic acid per day starting one month before the time they plan to become pregnant and throughout the first three months of pregnancy, unless contraindicated. Women should be advised not to attempt to achieve the 4000 µg daily dosage of folic acid by taking over-the-counter or prescription multivitamins containing folic acid because of the possibility of ingesting harmful levels of other vitamins, for example, Vitamin A. It should be noted that 4000 µg of folic acid did not prevent all neural tube defects in the MRC study. Therefore, high-risk patients should be cautioned that folic acid supplementation does not preclude the need for counseling or consideration of prenatal testing for neural tube defects.

Table 3. Dietary Reference Intake for Women^{1,5,6}

Nutrient	Adult Women	Pregnancy	Lactation
Biotin	25 to 30 µg	30 µg	35 µg
Folate	400 µg DFE	600 µg DFE	500 µg DFE
Niacin	14 mg	18 mg	17 mg
Pantothenic acid	5 mg	6 mg	7 mg
Riboflavin	1.0 to 1.1 mg	1.4 mg	1.6 mg
Thiamin	1.0 to 1.1 mg	1.4 mg	1.4 mg
Vitamin A	700 µg RAE	750 to 770 µg RAE	1,200 to 1,300 µg RAE
Vitamin B ₆	1.2 to 1.3 mg	1.9 mg	2.0 mg
Vitamin B ₁₂	2.4 µg	2.6 µg	2.8 µg

Nutrient	Adult Women	Pregnancy	Lactation
Vitamin C	65 to 75 mg	80 to 85 mg	115 to 120 mg
Vitamin D	15 to 20 µg	15 µg	15 µg
Vitamin E	15 mg	15 mg	19 mg
Vitamin K	75 to 90 µg	75 to 90 µg	75 to 90 µg
Calcium	1,000 to 1,300 mg	1,000 to 1,300 mg	1,000 to 1,300 mg
Choline	400 to 425 mg	450 mg	550 mg
Chromium	24 to 25 µg	29 to 30 µg	44 to 45 µg
Copper	890 to 900 µg	1,000 µg	1,300 µg
Fluoride	3 mg	3 mg	3 mg
Iodine	150 µg	220 µg	290 µg
Magnesium	310 to 360 mg	350 to 400 mg	310 to 360 mg
Iron	15 to 18 mg	27 mg	9 to 10 mg
Manganese	1.6 to 1.8 mg	2.0 mg	2.6 mg
Molybdenum	43 to 45 µg	50 µg	50 µg
Phosphorus	700 to 1,250 mg	700 to 1,250 mg	700 to 1,250 mg
Selenium	55 µg	60 µg	70 µg
Zinc	8 to 9 mg	11 to 12 mg	12 to 13 mg
Alpha-linolenic acid	1.1 g	1.4 g	1.3 g
Linoleic acid	11 to 12 g	13 g	13 g

DFE=dietary folate equivalents, RAE=retinol activity equivalents

III. Indications

Indications for the prenatal vitamins are noted in Table 4. Dietary supplements do not need approval from the Food and Drug Administration (FDA) before they are marketed. These drugs have not been found by the FDA to be safe and effective, and the labeling has not been approved by the FDA.

Table 4. Indications for the Prenatal Vitamins¹⁶⁻¹⁸

Generic Name(s)	Nutritional supplement for use prior to conception, throughout pregnancy and during the postnatal period	Nutritional supplement to help ease nausea and vomiting of pregnancy
Iron, folic acid, multivitamins with minerals	✓	
Prenatal vitamins, folic acid	✓	
Prenatal vitamins, folic acid, ginger oil		✓
Prenatal vitamins, iron, folic acid	✓	
Prenatal vitamins, iron, folic acid, DHA	✓	
Prenatal vitamins, iron, folic acid, docusate	✓	
Prenatal vitamins, iron, folic acid, omega-3 fatty acids	✓	
Prenatal vitamins, iron, folic acid, selenium	✓	
Prenatal vitamins, iron, folic acid, vitamin B6	✓	
Prenatal vitamins, iron, folic acid, DHA, docusate	✓	
Prenatal vitamins, iron, folic acid, DHA, EPA	✓	
Prenatal vitamins, iron, folic acid, DHA, fish oil	✓	
Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids	✓	
Prenatal vitamins, iron, folic acid, docusate, omega-3 fatty acids	✓	
Prenatal vitamins, iron, folic acid, DHA, docusate, ubidecarenone	✓	
Prenatal vitamins, iron, folic acid, DHA, docusate, EPA, fish oil	✓	
Prenatal vitamins, iron, folic acid, DHA, EPA,	✓	

Generic Name(s)	Nutritional supplement for use prior to conception, throughout pregnancy and during the postnatal period	Nutritional supplement to help ease nausea and vomiting of pregnancy
omega-3 fatty acids		
Prenatal vitamins, iron, L-methylfolate	✓	
Prenatal vitamins, iron, L-methylfolate, DHA, EPA, omega-3 fatty acids	✓	

DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid

IV. Pharmacokinetics

There is limited or no data available on the pharmacokinetic properties of the prenatal vitamins.¹⁶⁻¹⁸

V. Drug Interactions

There are no significant drug interactions reported with the prenatal vitamins.¹⁶⁻¹⁸

VI. Adverse Drug Events

Adverse reactions with iron therapy may include anorexia, constipation, diarrhea, nausea, vomiting, dark stools and abdominal pain, which are usually transient. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.¹⁶⁻¹⁸ Accidental overdose of iron containing products is a leading cause of fatal poisoning in children under the age of six. The boxed warning for the prenatal vitamins is listed in Table 5.

Table 5. Boxed Warning for the Prenatal Vitamins¹⁶⁻¹⁸

WARNING
Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under six. Keep this product out of the reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

VII. Dosing and Administration

The usual dosing regimens for the prenatal vitamins are listed in Table 6.

Table 6. Usual Dosing Regimens for the Prenatal Vitamins¹⁶⁻¹⁸

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Iron, folic acid, multivitamins with minerals	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 50-1.25 mg
Prenatal vitamins, folic acid	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Chewable tablet: 1 mg
Prenatal vitamins, folic acid, ginger oil	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 1-500 mg
Prenatal vitamins, iron, folic acid	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 40-1.25 mg 85-1 mg 106-1 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			Chewable tablet: 29-1 mg 40-1 mg Tablet: 15-1 mg 18-1 mg 20-1 mg 27-1 mg 28-1 mg 28-6-1 mg 29-1 mg 30-20-1 mg 32-1 mg 60-1 mg 65-1 mg 66-1 mg
Prenatal vitamins, iron, folic acid, DHA	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 1.5-8.73-6.4 mg 10-1-200 mg 18-1-300 mg 18-1-350 mg 20-1-320 mg 22-6-1-200 mg 27-1-300 mg 27-1-400 mg 27.5-1-200 mg 28-1-200 mg 28-1-250 mg 28-1-300 mg 28-1-400 mg 29-1-200 mg 31-1-200 mg 32-1.25-110 mg 35-5-1-200 mg Combination package: 22-6-1-200 mg 28-6-1-200 mg 29-1-200 mg 29-1-250 mg 32-1-230 mg 65-1-250 mg
Prenatal vitamins, iron, folic acid, docusate	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 27-1-50 mg 29-1-25 mg 90-1-50 mg
Prenatal vitamins, iron, folic acid, omega-3 fatty acids	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 27-1-330 mg 28-1-200 mg 30-10-1-200 mg 30-1-310.1 mg 35-1-200 mg Combination package:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			27-1-374 mg 27-1-430 mg 29-1-250 mg 29-1-400 mg 29-1-430 mg
Prenatal vitamins, iron, folic acid, selenium	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 27 mg-1 mg-20 µg
Prenatal vitamins, iron, folic acid, vitamin B6	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 20-1-25 mg
Prenatal vitamins, iron, folic acid, DHA, docusate	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 26-1.2-55-300 mg 27-1-50-250 mg 27-1-50-260 mg 27-1.25-55-300 mg 29-1-50-265 mg 29-1.25-55-325 mg 29-1.25-55-350 mg 30-1-50-200 mg 30-1-50-260 mg 30-1.2-55-265 mg Combination package: 27-1-50-250 mg 30-1-50-300 mg 35-1-50-300 mg
Prenatal vitamins, iron, folic acid, DHA, EPA	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Combination package: 32-1-120-180 mg
Prenatal vitamins, iron, folic acid, DHA, fish oil	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 40-10-1-300-476 mg
Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Combination package: 27-1-250-312 mg
Prenatal vitamins, iron, folic acid, docusate, omega-3 fatty acids	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 27-1-50-500 mg
Prenatal vitamins, iron, folic acid, DHA, docusate, ubidecarenone	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 15-0.5-25-50-50 mg
Prenatal vitamins, iron, folic acid, DHA, docusate, EPA, fish oil	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 27-1-25-500 mg (215-45 mg)
Prenatal vitamins, iron, folic acid, DHA, EPA, omega-3 fatty acids	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Chewable tablet: 3.33-0.33-34.83 mg (25-5.1-4.73 mg)
Prenatal vitamins, iron, L-methylfolate	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Chewable tablet: 4.5-1 mg
Prenatal vitamins, iron, L-methylfolate, algal oil blend, soy	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 27-1.13-581.28 mg
Prenatal vitamins, iron, L-methylfolate, omega-3 fatty	Administer once daily.	Safety and effectiveness have not been established	Combination package: 4.5-1-150-37.5-75 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
acids, DHA, EPA		in pediatric patients.	

DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the prenatal vitamins are summarized in Table 7. There were no studies found in the medical literature that directly compared the various prenatal vitamin preparations.

Table 7. Comparative Clinical Trials with the Prenatal Vitamins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Gupta et al.²⁰ (2007)</p> <p>Multivitamin supplementation plus folic acid 500 µg/day and iron 60 mg/day</p> <p>vs</p> <p>placebo plus supplementation with folic acid 500 µg/day and iron 60mg/day</p>	<p>DB, PC, RCT</p> <p>Pregnant women between 24 to 32 weeks gestation with a BMI <18.5 and/or a hemoglobin level 7 to 9 g/dL</p>	<p>N=200</p> <p>Median 52 to 58 days</p>	<p>Primary: Birth weight, length, midarm, circumference, incidence of low birth weight, and early neonatal morbidity</p> <p>Secondary: Not reported</p>	<p>Primary</p> <p>Infants in the micronutrient supplement group were 98 g heavier (95% CI, -16 to 213) and 0.8 cm longer (95% CI, 0.03 to 1.57) than infants born to mothers who received placebo.</p> <p>Infants in the micronutrient supplement group were 0.2 cm larger in midarm circumference (95% CI, 0.04 to 0.36) than infants born to mothers who received placebo.</p> <p>Incidence of low birth weight decreased from 43.1 to 16.2% in those infants whose mothers received micronutrient supplementation (RR, 0.3; 95% CI, 0.13 to 0.71; P=0.006) compared to infants whose mothers received placebo.</p> <p>Early neonatal morbidity decreased from 28.0 to 14.8% in those infants whose mothers received micronutrient supplementation (RR, 0.42; 95% CI, 0.19 to 0.94; P=0.04) compared to infants whose mothers received placebo.</p> <p>Women who were anemic were not likely to benefit more from multivitamin supplementation in terms of birth size.</p> <p>There was no significant difference between birth size for women with hemoglobin levels of less than 9 g/dL and the rest in the micronutrient group.</p> <p>Secondary: Not reported</p>
<p>Liu et al.²¹ (2013)</p>	<p>DB, RCT</p> <p>Pregnant women in</p>	<p>N=18,775</p> <p>Variable</p>	<p>Primary: Perinatal mortality</p>	<p>Primary: The perinatal mortality rate was 8.76 of 1000 births for the folic acid group, 8.73 of 1000 for the iron–folic acid group, and 8.25 of 1000 for the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Folic acid vs iron-folic acid vs multiple micronutrients (MMN)</p>	<p>rural China ≥ 20 years old, ≤ 20 weeks gestation, nulliparous, hemoglobin > 10.0 g/dL, and had not consumed micronutrient supplements other than folic acid in the prior 6 months</p>	<p>duration</p>	<p>Secondary: Neonatal deaths, infant deaths, maternal hemoglobin and anemia, birth weight, birth length, duration of gestation</p>	<p>MMN group. Compared with prenatal folic acid alone, neither iron–folic acid (RR, 1.00; 95% CI, 0.68 to 1.46; P=0.99) nor MMN supplements (RR, 0.94; 95% CI, 0.64 to 1.39; P=0.76) affected the risk of perinatal mortality. Compared with iron–folic acid, MMN did not affect the risk of perinatal mortality (RR, 0.94; 95% CI, 0.64 to 1.39; P=0.77).</p> <p>Secondary: Risk of stillbirths, early neonatal deaths, neonatal deaths, or infant deaths did not differ by supplement group. Compared with folic acid alone, iron–folic acid and MMN increased third-trimester maternal hemoglobin concentration by 0.04 and 0.06 g/dL, respectively, and decreased the anemia prevalence by 28 and 29%, respectively, with a number needed to treat of 47 (95% CI, 33 to 81) for the iron–folic acid group and 46 (95% CI, 32 to 77) for the MMN group. Neither gestation duration nor birth weight or length differed significantly by supplement group.</p>
<p>Haider et al.²² (2006) Multiple micronutrient supplementation of 3 or more micronutrients vs placebo, no supplementation or supplementation with 2 or less micronutrients</p>	<p>MA (9 RCTs) Pregnant women (varying duration of pregnancies)</p>	<p>15,378 Duration not specified</p>	<p>Primary: Preterm birth, small for gestational age, low birth weight, premature rupture of membranes, preeclampsia, miscarriage, maternal mortality, perinatal mortality</p> <p>Secondary: Maternal anemia</p>	<p>Primary: A significant decrease in the number of low birth weight babies was observed when comparing multiple micronutrient supplementation to placebo, no supplementation or two or less micronutrients (RR, 0.83; 95% CI, 0.76 to 0.91).</p> <p>No significant differences were observed in preterm birth and perinatal mortality (RR, 0.92; 95% CI, 0.82 to 1.04).</p> <p>When multiple micronutrient supplementation was compared to iron and folic acid supplementation, no significant differences were observed in any primary outcome.</p> <p>Secondary: A significant decrease in maternal anemia was observed when comparing multiple micronutrient supplementation with placebo, no supplementation or supplementation of two or less micronutrients (RR, 0.61; 95% CI, 0.52 to 0.71).</p> <p>No significant differences were observed in maternal anemia when multiple micronutrient supplementation was compared to iron and folic acid supplementation (RR, 1.23; 95% CI, 0.82 to 1.83).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Lumley et al.²³ (2000)</p> <p>Multivitamins</p> <p>vs</p> <p>folate</p> <p>vs</p> <p>multivitamins plus folate</p>	<p>MA (4 RCTs)</p> <p>Periconceptual women</p>	<p>N=6,425</p> <p>Variable duration</p>	<p>Primary: NTD</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>Periconceptual folate supplementation reduced the prevalence of neural tube defects (RR, 0.28; 95% CI, 0.13 to 0.58). The reduction is similar for the first occurrence of defects (RR, 0.07; 95% CI, 0.00 to 1.32) and for recurrent defects (RR, 0.31; 95% CI, 0.14 to 0.66). The number needed to treat for folate prevention of an NTD is 847.</p> <p>The trials had very low power to identify differences in limb reduction defects (RR, 0.59; 95% CI 0.04 to 8.34), conotruncal defects (RR, 0.74; 95% CI, 0.16 to 3.32), orofacial clefts (RR, 0.76; 95% CI, 0.24 to 2.37) or all other major birth defects combined (RR, 0.76; 95% CI, 0.38 to 1.51).</p> <p>Folate supplementation was not associated with an increase in conception (RR, 1.02; 95% CI 0.97 to 1.07).</p> <p>No adverse effects of the folate supplementation were detected in terms of an increase in miscarriage (RR, 1.12; 95% CI, 0.98 to 1.29), or ectopic pregnancy (RR, 1.09; 95% CI, 0.47 to 2.55). There was no reduction in stillbirths (RR, 0.78; 95% CI, 0.34 to 1.78).</p> <p>There was no statistically significant reduction in NTD when multivitamins alone were compared with placebo (RR, 0.61; 95% CI, 0.26 to 1.45), when multivitamins were compared with multivitamins plus folate (RR, 2.05; 95% CI, 0.67 to 6.26), or when folate was compared with multivitamins plus folate (RR, 0.49; 95% CI, 0.09 to 2.66). When folate alone was compared with multivitamins alone there was a reduction with folate (RR, 0.27; 95% CI, 0.07 to 1.08), however this was not significant.</p> <p>Secondary: Not reported</p>
<p>Siege-Riz et al.²⁴ (2006)</p> <p>Multivitamin supplementation containing 30 mg of elemental iron</p>	<p>RCT</p> <p>Pregnant women who were less than 20 weeks of gestation with hemoglobin levels</p>	<p>N=429</p> <p>>9 weeks</p>	<p>Primary: Third trimester iron status, birth weight, preterm birth, and small-for-gestational age</p>	<p>Primary:</p> <p>There were no significant differences between the treatment groups in any of the iron status indicators measured.</p> <p>Women who received iron supplementation gave birth to infants who weighed 108 g heavier than women who did not receive iron supplementation (P=0.03).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(ferrous sulfate) vs multivitamin supplementation without iron	≥110 g/L and ferritin levels ≥40 µg/L		Secondary: Not reported	There were no significant differences among women who received iron supplementation compared to those who did not receive iron supplementation for the following outcomes: gestational age at delivery (P=0.43), low birth weight (4.8 vs 9.5%, respectively; P=0.09), preterm delivery (7.5 vs 13.9%, respectively; P=0.05), or small-for-gestational age (P=0.22). Secondary: Not reported
Goh et al. ²⁵ (2006) Prenatal multivitamin supplementation	MA (6RCTs) Pregnant women	N=not specified Variable duration	Primary: Risk of pediatric cancer Secondary: Not reported	Primary: Use of prenatal multivitamins by the pregnant mothers was associated with a protective effect for childhood leukemia (OR, 0.64; 95% CI 0.53 to 0.78). Ingestion of prenatal multivitamins was associated with a protective effect for acute lymphoblastic leukemia (OR, 0.61; 95% CI, 0.50 to 0.74). There was only one study that reported information regarding acute myeloid leukemia which suggested a protective effect of prenatal multivitamin use. Supplementation with prenatal vitamins was associated with a decreased risk for neuroblastoma (OR, 0.53; 95% CI, 0.42 to 0.68). Prenatal supplementation was associated with decreased risk for pediatric brain tumors (OR, 0.73; 95% CI, 0.60 to 0.88) Secondary: Not reported
Hofmeyr et al. ²⁶ (2006) Calcium supplementation (1.5 to 2 g/day)	MA (12 RCTs) Pregnant women	N=15,206 Variable duration	Primary: Hypertensive disorders of pregnancy and related maternal and child outcomes	Primary: There was less high blood pressure with calcium supplementation rather than placebo (RR, 0.70; 95% CI, 0.57 to 0.86). There was a reduction in the risk of pre-eclampsia (RR, 0.48; 95% CI, 0.33 to 0.69).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Secondary: Not reported	<p>The relative risk of having the composite outcome maternal death or serious morbidity was reduced for women allocated calcium supplementation compared with placebo (RR, 0.80; 95% CI, 0.65 to 0.97).</p> <p>There was no difference in the rate of placental abruption between the groups (RR, 0.86; 95% CI, 0.55 to 1.34).</p> <p>There was no significant effect on the relative risk of caesarean section (RR, 0.95; 95% CI, 0.88 to 1.01).</p> <p>There was no overall difference in proteinuria between groups (RR, 1.04; 95% CI, 0.86 to 1.26).</p> <p>There was no difference in the rate of severe pre-eclampsia (RR, 0.74; 95% CI, 0.48 to 1.15) or eclampsia between the groups (RR, 0.73; 95% CI, 0.41 to 1.27).</p> <p>There was no difference in maternal deaths between the groups (RR, 0.17; 95% CI, 0.02 to 1.39).</p> <p>There was no overall effect on preterm birth (RR, 0.81; 95% CI, 0.64 to 1.03).</p> <p>There was no overall effect on the risk of having a baby with birthweight less than 2,500 g (RR, 0.84; 95% CI, 0.68 to 1.03).</p> <p>There was no overall effect on the relative risk of the baby being born small-for-gestational age (RR, 1.10; 95% CI, 0.88 to 1.37).</p> <p>There was no overall effect on the relative risk of admission to a neonatal intensive care unit (RR, 1.05; 95% CI, 0.94 to 1.18).</p> <p>There was no overall effect on the relative risk of a stillbirth or the baby dying before discharge from hospital (RR, 0.89; 95% CI, 0.73 to 1.09).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Helland et al.²⁷ (2008)</p> <p>Omega-3 fatty acids in the form of cod liver oil (containing 1,183 mg of DHA and 803 mg of EPA) 10 mL/day from 18 weeks of pregnancy until 3 months after delivery</p> <p>vs</p> <p>corn oil (containing 4,747 mg of linoleic acid and 92 mg of ALA) 10 mL/day from 18 weeks of pregnancy until 3 months after delivery</p>	<p>DB, RCT</p> <p>Healthy pregnant women 19 to 35 years of age</p>	<p>N=143</p> <p>7 year follow-up of children born to pregnant women receiving treatment intervention</p>	<p>Primary: Cognitive function using the Kaufman Assessment Battery for Children</p> <p>Secondary: Not reported</p>	<p>Primary: There were no significant differences in Kaufman Assessment Battery for Children cognitive scores at seven years of age among children whose mothers received cod liver oil during pregnancy as compared to children whose mothers received corn oil during pregnancy.</p> <p>Maternal plasma levels of ALA and DHA at 35 weeks of pregnancy were positively associated with sequential processing scale at age seven.</p> <p>There was no significant correlation between fatty acid status at birth and BMI at age seven.</p> <p>Secondary: Not reported</p>
<p>Dunstan et al.²⁸ (2008)</p> <p>Fish oil (2.2 g DHA and 1.1 g EPA per day) from 20 weeks' gestation until delivery</p> <p>vs</p>	<p>DB, RCT</p> <p>Pregnant women</p>	<p>N=98</p> <p>2.5 year follow-up of children born to pregnant women receiving treatment intervention</p>	<p>Primary: Effects on infant growth and developmental quotients (Griffiths Mental Development Scales), receptive language (Peabody Picture Vocabulary Test) and behavior</p>	<p>Primary: There was no significant difference in growth measurements between the fish oil group and the olive oil group. The mean age for both groups was 30 months; the mean height was 93.8 cm for the fish oil group vs 93.3 cm for the olive oil group (P=0.642); the mean weight was 14.5 vs 14.1 kg, respectively (P=0.456); and the head circumference was 49.4 vs 49.8 cm, respectively (P=0.304).</p> <p>Children from the fish oil group attained a significantly higher score for eye and hand coordination (P=0.021).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
olive oil from 20 weeks' gestation until delivery			(Child Behavior Checklist) Secondary: Not reported	There was no significant difference mean standard score obtained in the Peabody Picture Vocabulary Test between the fish oil group and the olive oil group (P=0.110). Results from the Child Behavior Checklist indicated no significant differences between the mean T scores of the fish oil and olive oil groups for internalizing (P=0.576), externalizing (P=0.706), total problem behavior scales (P=0.548), mean length of phrases (P=0.300) and vocabulary centile score (P=0.650). Secondary: Not reported
Makrides et al. ²⁹ (2006) Marine oil supplement (DHA and EPA dose ranged from 133 mg to 3 g per day) vs placebo or no treatment	MA (6 RCTs) Pregnant women	N=2,783 Variable follow-up	Primary: Risk of pre-eclampsia, preterm birth, and birth weight Secondary: Not reported	Primary: There were no differences in the risk of high blood pressure (RR, 1.09; 95% CI, 0.90 to 1.33) or the incidence of pre-eclampsia (RR, 0.86; 95% CI, 0.59 to 1.27) between marine oil-treated and control groups. Women allocated to a marine oil supplement had a mean gestation that was 2.6 days longer than women allocated to placebo or no treatment (difference, 2.55 days; 95% CI, 1.03 to 4.07 days). This was not reflected in a clear difference between the two groups in the relative risk of birth before 37 completed weeks (RR, 0.92; 95% CI, 0.79 to 1.07). Women allocated to marine oil had a lower risk of giving birth before 34 completed weeks' gestation compared with placebo (RR, 0.69; 95% CI, 0.49 to 0.99). Birthweight and birth length were slightly greater in infants born to women in the marine oil group compared with control. However, there was no overall difference between the groups in the relative risk for low birthweight or small-for-gestational babies. Secondary: Not reported
Carlson et al. ³⁰ (2013)	DB, PC, RCT Women between 8	N=350 Enrollment	Primary: Red blood cell (RBC)-	Primary: RBC-phospholipid-DHA (percentage of total fatty acids by weight) was significantly higher in the DHA-supplemented group at birth and increased

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>3 capsules/day of a marine algae-oil source of DHA (200 mg DHA/capsule)</p> <p>vs</p> <p>placebo group received 3 capsules containing half soybean and half corn oil</p>	<p>and 20 weeks of gestation, between 16 and 35.99 years of age, and planning to deliver at a hospital in the Kansas City metropolitan area</p>	<p>until birth</p>	<p>phospholipid-DHA content, gestation duration, birth weight and length</p> <p>Secondary: Low and very low birth weight</p>	<p>significantly from enrollment only in that group (P<0.001). Gestational age was also 2.87 days greater (P=0.041), and birth weight and length were higher by 172 grams and 0.7 cm, respectively (P=0.004 and P=0.022, respectively).</p> <p>Secondary: Cord RBC-phospholipid-DHA and head circumference were significantly higher in newborns of women assigned to DHA than to placebo. The incidence of preterm birth did not differ between the groups; however, significantly more infants in the placebo group had an early preterm birth (P=0.025). A trend toward fewer low birth weight deliveries was not statistically significant (P=0.059), but there was a significantly lower incidence of very low birth weight in the DHA-supplemented group (P=0.026).</p>
<p>Gould et al.³¹ (2014)</p> <p>Three 0.5 gram DHA-rich capsules/day, which provided 800 mg DHA/day and 100 mg EPA/day</p> <p>vs</p> <p>three 0.5 gram capsules that contained a blend of vegetable oils</p>	<p>DB, RCT</p> <p>Women with singleton pregnancies of 18 to 21-week gestation with no fetal abnormalities</p>	<p>N=184</p> <p>Enrollment to delivery; follow-up when child 27 months of age</p>	<p>Primary: Average time it took to be distracted when playing with a toy (distractibility) and the accuracy of remembering a new hiding location while inhibiting a learned response to search in the previous location (working memory and inhibitory control [WMIC])</p> <p>Secondary: Not reported</p>	<p>Primary: The primary outcome of distractibility did not differ between treatment and control groups. The primary outcome of the WMIC did not differ between treatment and control groups. However, the control group were more accurate at searching for the hidden toy during training trials than was the treatment group (14.4 mm; 95% CI, 20.2 to 29.1 mm; P=0.05).</p> <p>Secondary: Not reported</p>
<p>Makrides et al.³²(2010)</p>	<p>DB, MC, RCT</p> <p>Pregnant women</p>	<p>N=2,399 (women)</p>	<p>Primary: High level of maternal</p>	<p>Primary: No significant differences were observed between groups in the percentage of women with high levels of depressive symptoms through six</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>DHA supplementation (800 mg of DHA and 100 mg of EPA)</p> <p>vs</p> <p>vegetable oil capsules without DHA</p>	<p>with singleton pregnancies less than 21 weeks gestation</p>	<p>N=726 (children)</p> <p>6 months postpartum</p>	<p>depressive symptoms as documented by a score >12 on the Edinburgh Postnatal Depression Scale at six weeks or six months postpartum, neurodevelopment at 18 months of age</p> <p>Secondary: Percentage of women medically diagnosed with depression or receiving treatment for depression during pregnancy, at six weeks and six months postpartum</p>	<p>months postpartum (RR, 0.85; 95% CI, 0.70 to 1.02).</p> <p>No significant differences were observed between groups in mean cognitive composite scores or mean language composite scores (adjusted mean difference, 0.01; 95% CI, -1.36 to 1.37 and adjusted mean difference, -1.42; 95% CI, -3.07 to 0.22 respectively).</p> <p>Secondary: No difference was observed between groups in the percentage of women medically diagnosed with depression or receiving treatment for depression during the trial.</p>
<p>Lewin et al.³³ (2005)</p> <p>Omega-3 fatty acid supplementation</p> <p>vs</p> <p>placebo or no treatment</p>	<p>MA</p> <p>Pregnant women, breastfeeding mothers, preterm and term infants</p>	<p>89 RCT</p> <p>Variable duration</p>	<p>Primary: Safety issues, pregnancy outcomes, growth pattern outcomes, neurological development outcomes, visual function outcomes, cognitive development outcomes</p>	<p>Primary: <i>Safety</i> Omega-3 fatty acids supplementation in pregnant women, breastfeeding mothers, and preterm and term infants, was very well tolerated and did not generate any serious adverse events across the included RCTs.</p> <p><i>Pregnancy Outcomes</i> There was no significant difference between intervention groups in the duration of gestation measured as mean of gestational age at delivery.</p> <p>Omega-3 fatty acids did not have a significant effect on the proportion of premature deliveries.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>Secondary: Not reported</p>	<p>There is inconsistent evidence of the use of omega-3 fatty acids supplements during the second or third trimester of pregnancy to reduce the incidence of premature pregnancies in high- and low-risk populations. The overall effect does not show a significant difference between study arms.</p> <p>Supplementation with omega-3 fatty acids did not have a significant effect on the incidence of preeclampsia.</p> <p>There was no significant difference in the incidence of gestational hypertension between treatment groups (OR, 1.07; 95% CI, 0.75 to 1.51).</p> <p>The mean birth weight was not influenced by the intervention.</p> <p><i>Growth Pattern Outcomes</i> There was no statistical difference between infants from mothers that were taking the supplementation with omega-3 and omega-6, or omega-6 fatty acids predominantly, on the weight, length, and head circumference from birth to 12 months of age.</p> <p>There was no effect of breast milk, with maternal intake of omega-3 (DHA) or omega-6 fatty acids, on the growth patterns at any time point.</p> <p><i>Neurological Development Outcomes</i> One study failed to find a significant difference between groups in maturity as evaluated from the EEGs, neither at day one of life nor at three months of age.</p> <p>Two studies showed that maternal breast milk may not have an influence on the neurological outcome, measured with the Psychomotor Development Index scale of the Bayley's Index.</p> <p><i>Visual Function Outcomes</i> One study failed to find a significant effect of DHA supplementation during pregnancy on the retinal sensitivity measured at birth in term infants. One cross-sectional study failed to find a statistically significant</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>difference in mean visual function values between the exclusively breastfed group and the infants who were also receiving formula.</p> <p>Five studies found that the correlation between the DHA content in breast milk and visual function was not consistent with the clinical outcomes measured in breastfed term infants of mothers who were or were not taking supplements containing high DHA.</p> <p><i>Cognitive Development Outcomes</i> There were no differences between groups in the novelty preference (Fagan Test of Infant Intelligence) at six and nine months of age.</p> <p>Two studies of breastfed children failed to find a difference in the mean Bayley's Mental Developmental Index score between groups at one or two years of age.</p> <p>Secondary: Not reported</p>
<p>Harper et al.³⁴ (2010)</p> <p>Omega-3 fatty acid supplementation (800 mg of DHA and 1,200 mg of EPA)</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, RCT</p> <p>Pregnant women between 16 and 22 weeks gestation with a history of previous singleton preterm birth</p>	<p>N=852</p> <p>14 to 20 weeks</p>	<p>Primary: Delivery before 37 weeks gestation</p> <p>Secondary: Delivery before 35 weeks, delivery before 32 weeks, spontaneous preterm delivery, medically indicated preterm delivery, delivery after 40 weeks</p>	<p>Primary: No significant difference was observed between groups in the risk of delivery before 37 weeks (RR, 0.91; 95% CI, 0.77 to 1.07).</p> <p>Secondary: No significant differences were observed between groups for any secondary outcome measure.</p>
<p>Szajewska et al.³⁵ (2006)</p> <p>Omega-3 fatty acid supplementation</p>	<p>MA (6 RCTs)</p> <p>Pregnant women</p>	<p>N=1,278</p> <p>Variable duration</p>	<p>Primary: Pregnancy and related maternal and child outcomes</p>	<p>Primary: Omega-3 supplementation was associated with a significantly greater duration of pregnancy (difference, 1.57 days; 95% CI, 0.35 to 2.78).</p> <p>There was no significant difference between supplemented and non-</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>Secondary: Not reported</p>	<p>supplemented subjects in the percentage of preterm deliveries (RR, 0.67; 95% CI, 0.41 to 1.10) or in the rate of low birth weight (RR, 0.66; 95% CI, 0.34 to 0.26).</p> <p>There was no significant difference between supplemented and non-supplemented subjects in the rate of preeclampsia or eclampsia (RR, 0.73; 95% CI, 0.22 to 2.37) or in the rate of cesarean delivery (RR, 1.17; 95% CI, 0.79 to 1.74).</p> <p>There was no significant difference between supplemented and non-supplemented subjects in the rate of gestational diabetes (RR, 0.73; 95% CI, 0.22 to 2.37).</p> <p>There was no significant difference between supplemented and non-supplemented subjects in the placental weight (difference, 10.9 g; 95% CI, 10.4 to 32.2).</p> <p>There was no significant difference in birth weight between supplemented and non-supplemented control subjects (difference, 54 g; 95% CI, -3.1 to 111).</p> <p>There was no significant difference between supplemented and non-supplemented subjects in the length at birth (difference, 0.23 cm; 95% CI, -0.04 to 0.5).</p> <p>Supplementation was associated with significantly greater head circumference of the infants in the supplemented group, as compared with those of the non-supplemented control group (difference, 0.26 cm; 95% CI, 0.02 to 0.49).</p> <p>Secondary: Not reported</p>

Study design abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, RCT=randomized controlled trial

Miscellaneous abbreviations: ALA= α -linolenic acid, BMI=body mass index, CI=confidence interval, DHA=docosahexaenoic acid, EEG=electroencephalogram, EPA=eicosapentaenoic acid, NTD=neural tube defect, OR=odds ratio, RR=relative risk

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 8. Relative Cost of the Prenatal Vitamins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Iron, folic acid, multivitamins with minerals	Tablet	OB Complete®	\$\$\$\$	\$
Prenatal vitamins, folic acid	Chewable tablet	Prenate®	\$\$\$\$	N/A
Prenatal vitamins, folic acid, ginger oil	Tablet	Prenate AM®	\$\$\$\$	N/A
Prenatal vitamins, iron, folic acid	Capsule, chewable tablet, tablet	Concept OB®*, Nestabs®*, Niva-Plus®*, OB-Complete Premier®, Prefera OB®*, Prenata®, Prenate Elite®, Prenate Star®, Provida OB®, Select-OB®, Thrivite Rx®*, Tricare®, Vinate II®, Vinate Care®, Vitafof Nano®, Vitafof-OB®	\$\$\$	\$
Prenatal vitamins, iron, folic acid, DHA	Capsule, chewable tablet, combination package	Active OB®, Enbrace HR®, Natelle One®*, Nestabs DHA®*, OB Complete Petite®, OB Complete Gold®, Prefera-OB One®, Prefera-OB Plus DHA®, Prenate DHA®,	\$\$\$	\$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
		Prenate Enhance [®] , Prenate Essential [®] , Prenate Mini [®] , Prenate Pixie [®] , Prenate Restore [®] , Primacare [®] , Provida DHA [®] , Select-OB+DHA [®] , Tristart DHA [®] , Vitafol-OB+DHA [®] , Vitafol-One [®] , Vitafol Ultra [®]		
Prenatal vitamins, iron, folic acid, docusate	Tablet	Citranatal RX [®]	\$\$\$	N/A
Prenatal vitamins, iron, folic acid, omega-3 fatty acids	Capsule, combination package	Bal-Care DHA Essential ^{®†} , Concept DHA ^{®*} , OB Complete With DHA [®] , PR Natal 400 ^{®*} , PR Natal 430 [®] , PR Natal 400 EC [®] , PR Natal 430 EC [®] , Relnate ^{®*}	\$\$\$	\$
Prenatal vitamins, iron, folic acid, selenium	Tablet	Vinate-M ^{®*}	\$	\$
Prenatal vitamins, iron, folic acid, vitamin B6	Tablet	Citranatal B-Calm [®]	\$	\$
Prenatal vitamins, iron, folic acid, DHA, docusate	Capsule, combination package	Citranatal 90 DHA ^{®*} , Citranatal Assure ^{®*} , Citranatal DHA [®] , Citranatal Harmony [®] , Nexa Plus [®] , Vitafol Fe + Docusate [®]	\$\$\$	\$
Prenatal vitamins, iron, folic acid, DHA, EPA	Combination package	Nestabs ABC [®]	\$\$	N/A
Prenatal vitamins, iron, folic acid, DHA, fish oil	Capsule	OB Complete One [®]	\$\$\$\$	N/A
Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids	Combination package	Prenatal Plus-DHA [®]	\$	N/A
Prenatal vitamins, iron, folic acid, docusate, omega-3 fatty acids	Capsule	N/A	N/A	N/A
Prenatal vitamins, iron, folic acid, DHA, docusate, ubidecarenone	Tablet	Preque 10 [®]	\$\$	N/A
Prenatal vitamins, iron, folic acid, DHA, docusate, EPA, fish oil	Capsule	Tricare Prenatal DHA One ^{®*}	\$\$\$	\$\$\$
Prenatal vitamins, iron, folic acid, DHA, EPA, omega-3 fatty acids	Chewable tablet	Vitafol Gummies [®]	\$\$	N/A
Prenatal vitamins, iron, L-methylfolate	Chewable tablet	Tricare Prenatal Chewable [®]	\$\$\$\$	N/A
Prenatal vitamins, iron, L-methylfolate, algal oil blend, soy [†]	Capsule	Vinate DHA RF ^{®†}	\$\$\$	N/A
Prenatal vitamins, iron, L-methylfolate, DHA, EPA, omega-3 fatty acids	Combination package	Tricare Prenatal with DHA [®]	\$	N/A

*Generic is available in at least one dosage form or strength.

† Clinical information for this product is not available in the various drug databases.

DHA=Docosahexaenoic acid

EPA=Eicosapentaenoic acid

N/A=Not available

X. Conclusions

Women of reproductive age should maintain good nutritional status prior to, during, and after pregnancy to minimize health risks to both the mother and child.¹⁻³ This includes maintaining a healthy weight, participating in physical activity, consuming a variety of foods to meet the Dietary Reference Intake recommendations, as well as appropriate and timely supplementation with multivitamins.¹⁻³

It is recommended that all women planning pregnancy take a supplement containing 400 to 800 µg of folic acid on a daily basis to reduce the risk of neural tube defects.^{1,7-11} Women should receive at least 27 mg of elemental iron per day during pregnancy; however, higher amounts are necessary for pregnant women with iron deficiency anemia.^{1-3,5,12} There is evidence that maternal consumption of folic acid-containing multivitamins may reduce the risk of neural tube defects, cardiac defects, urinary tract defects, limb defects, as well as other birth defects.^{2,13,52} The American Dietetic Association recommends supplementation with a multivitamin for pregnant women with iron deficiency anemia, poor-quality diets, those who consume no or small amounts of animal source foods, women carrying two or more fetuses, those who smoke or abuse alcohol or drugs, and for women who are infected with human immunodeficiency virus.¹ In addition to a well-balanced diet, supplementation with a folic acid-containing multivitamin should be encouraged in all women of reproductive age to help support healthy pregnancy outcomes.²

There are many different prenatal vitamins currently available. The majority of the products contain folic acid and iron, as well as various combinations of vitamins and minerals. Additional nutrients which have been added to some of the prenatal vitamins include aspartame, docusate, L-methylfolate, omega-3 fatty acids, and omega-6 fatty acids. Many of the prenatal vitamins are available in a generic formulation, including products which contain omega-3 fatty acids.

There were no clinical trials found in the medical literature that directly compared the various prenatal vitamin preparations. Supplementation with folic acid is clearly beneficial during pregnancy, and adequate intake of iron is necessary to reduce the risk of iron deficiency anemia. There has been recent interest in the health benefits associated with the use of supplemental omega-3 fatty acids during pregnancy. Omega-3 fatty acids are necessary for nervous tissue growth and function, and dietary intake has a variety of health benefits.¹⁴ Some studies have suggested that omega-3 fatty acids may improve fetal/neonatal visual and neural growth and help prevent low birth weight when taken as a supplement during pregnancy.^{2-3,15} Several meta-analyses have evaluated the use of supplemental omega-3 fatty acids during pregnancy. In general, the results of these analyses have not found a significant difference in pregnancy-related outcomes.^{27-29,33-35} This includes assessment of maternal outcomes (blood pressure, preeclampsia, and preterm delivery) and child outcomes (neurological development, growth patterns, visual function, and cognitive development).^{27-29,33,35} There is insufficient evidence regarding the supplemental use of omega-3 fatty acids and the effects on pregnancy-related maternal and child outcomes.

There is insufficient evidence to support that one brand prenatal vitamin is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand prenatal vitamin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Procter SB and Campbell CG; Academy of Nutrition and Dietetics. Position of The Academy of Nutrition and Dietetics: Nutrition and lifestyle for a healthy pregnancy outcome. *J Acad Nutr Diet*. 2014;114:1099-1103.
2. Gardiner P, Nelson L, Shellhaas C, et al. The clinical content of preconception care: nutrition and dietary supplements. *Am J Obstet Gynecol* 2008;199(Suppl 2):S345-S356.
3. Cox JT, Phelan ST. Nutrition during pregnancy. *Obstetrics and Gynecology Clinics of North America*. 2008;35:369-383.
4. US Department of Health and Human Services and US Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans; 2015 [cited 2017 Mar]. Available from: <http://health.gov/dietaryguidelines/2015/guidelines/>.
5. Institute of Medicine. Dietary Reference Intakes Tables and Application. Washington, CD: National Academy of Sciences; 2017 [cited 2017 Mar]. Available from: <http://www.nationalacademies.org/hmd/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx>.
6. Trumbo P, Schlicker S, Yates A, et al. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc* 2002;102:1621-30.
7. CDC. Recommendations to Improve Preconception Health and Health Care—United States. *MMWR Recommendations and Reports* 2006;55(RR-06):1-23.
8. U.S. Preventive Services Task Force. Folic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;150:626-631.
9. American College of Obstetricians and Gynecologists (ACOG). Neural tube defects. *ACOG practice bulletin* 44. *Obstet Gynecol* 2003;102:203-13.
10. No authors listed. Folic acid for the prevention of neural tube defects. American Academy of Pediatrics Committee on Genetics. *Pediatrics*. 1999 Aug;104(2 Pt 1):325-7.
11. American Academy of Family Physicians. Clinical Preventative Services: neural tube defects [guideline on the internet]. Leawood (KS): AAFP; 2009 [cited 2012 Sep]. Available from: <http://www.aafp.org/online/en/home/clinical/exam/neuraltubedefects.html>.
12. American College of Obstetricians and Gynecologists (ACOG). Anemia in pregnancy. *ACOG practice bulletin* 95. *Obstet Gynecol* 2008;112:201-207.
13. Goh Y, Bollane E, Elnarson T, et al. Prenatal multivitamin supplementation and rates of congenital anomalies: a meta-analysis. *J Obstet Gynecol Can* 2006;28:680-689.
14. Innis S. Dietary (n-3) fatty acids and brain development. *J Nutr*. 2007;137(4): 855-9.
15. Kris-Etherton P, Innis S. Position of the American Dietetic Association and Dietitians of Canada: Dietary fatty acids. *J Am Diet Assoc* 2007;107:1599-611.
16. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2014 [cited Oct 2014]. Available from: <http://online.factsandcomparisons.com>.
17. Multiple vitamins (prenatal): drug information. In: UpToDate, Basow DS (Ed), UpToDate, Waltham, MA, 2017.
18. Daily Med [database on the internet]. Bethesda (MD): National Library of Medicine; 2017 [cited 2017 Mar]. Available at: <http://dailymed.nlm.nih.gov/dailymed/about.cfm>.
- 19.
20. Gupta P, Ray M, Dua T. Multimicronutrient supplementation for undernourished pregnant women and the birth size of their offspring: a double-blind, randomized, placebo-controlled trial. *Arch Pediatr Adolesc Med*. 2007;161(1):58-64.
21. Liu J, Mei Z, Ye R, et al. Micronutrient supplementation and pregnancy outcomes. *JAMA Intern Med*. 2013;173(4):276-282.
22. Haider B, Bhutta Z. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art No.:CD004905. DOI: 10.1002/14651858.CD004905.pub2.
23. Lumley J, Watson L, Watson M, et al. Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects. *Cochrane Database Syst Rev* 2000; CD001056.
24. Siega-Riz AM, Hartzema AG, Turnbull C, et al. The effects of prophylactic iron given in prenatal supplements on iron status and birth outcomes: a randomized controlled trial. *Am J Obstet Gynecol*. 2006;194(2):512-9.
25. Goh Y, Bollane E, Elnarson T, et al. Prenatal multivitamin supplementation and rates of congenital anomalies: a meta-analysis. *J Obstet Gynaecol Can*. 2006;28:680-9.
26. Hofmeyr G, Atallah A, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2006;3 Art No CD001059.

27. Helland I, Smith L, Blomen B, et al. Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. *Pediatrics* 2008;122:e472-9.
28. Dunstan J, Simmer K, Dixon G, et al. Cognitive assessment of children at age 2 1/2 years after maternal fish oil supplementation in pregnancy: a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2008;93:45-50.
29. Makrides M, Duley L, Olsen SF. Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. *Cochrane Database Syst Rev*. 2006;(3):CD003402. DOI:10.1002/14651858.CD001059.pub2.
30. Carlson SE, Colombo J, Gajewski BJ, et al. DHA supplementation and pregnancy outcomes. *Am J Clin Nutr* 2013;97:808–815.
31. Gould JF, Makrides M, Colombo J, and Smithers LG. Randomized controlled trial of maternal omega-3 long-chain PUFA supplementation during pregnancy and early childhood development of attention, working memory, and inhibitory control. *Am J Clin Nutr* 2014;99:851–859.
32. Makrides M, Gibson R, McPhee A, et al. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. *JAMA*. 2010;304(15):1675-83.
33. Lewin G, Schachter H, Yuen D, et al. Effects of omega-3 fatty acids on child and maternal health. *Evid Rep Technol Assess* 2005; (118) Agency for Healthcare Research and Quality. Publication Number 05-E025-2.
34. Harper M, Thom E, Klebanoff M, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. *Obstet Gynecol*. 2010;115(2):234-42.
35. Szajewska H, Horvath A, Koletzke. Effect of n-3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth measure at birth: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2006;83:1337-44.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Immunomodulatory Agents used to treat Multiple Sclerosis
AHFS Class 922000
May 10, 2017

I. Overview

Several immunomodulatory agents are Food and Drug Administration (FDA)-approved for the treatment of adult patients with relapsing forms of multiple sclerosis (MS), including the injectable products daclizumab (Zinbryta[®]), glatiramer acetate (Copaxone[®], Glatopa[®]), natalizumab (Tysabri[®]), interferon β (IFN β)-1b (Betaseron[®], Extavia[®]), intramuscular (IM) IFN β -1a (Avonex[®]), subcutaneous (SC) IFN β -1a (Rebif[®]), SC peginterferon β -1a (Plegridy[®]) and the oral products dimethyl fumarate (Tecfidera[®]), fingolimod (Gilenya[®]), and teriflunomide (Aubagio[®]).¹⁻¹⁴

MS is a chronic and potentially disabling neurological disease characterized by repeated episodes of inflammation within the nervous tissue of the brain and spinal cord, resulting in injury to the myelin sheaths and subsequently the nerve cell axons.¹⁵⁻¹⁶ MS is an autoimmune inflammatory demyelinating disease of the central nervous system.¹⁵⁻¹⁶ There are four clinical subtypes of MS: relapsing-remitting (RRMS), primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive (SPMS).¹⁵⁻¹⁸ The most common form is RRMS, characterized by acute relapses followed by partial or full recovery.^{16,18} Patients with PPMS have a continuous and gradual decline in function without evidence of acute attacks. Patients with PRMS also have a continuous decline in function while experiencing occasional attacks. Finally, SPMS begins as RRMS, but as time progresses the attack rate declines and patients experience a gradual deterioration.¹⁸

The exact mechanisms of action of the immunomodulatory agents used to treat MS are generally not completely understood but are likely due to their antiproliferative and immuno-modulatory effects.¹⁻¹⁴ Daclizumab is a humanized monoclonal antibody that has specific binding activity for the alpha chain component of the high-affinity interleukin-2 receptor. Because of its safety risks, which include hepatotoxicity and serious infection, the use of daclizumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. Daclizumab is available only through a restricted distribution program. Patients should have baseline liver function testing before starting daclizumab, with testing repeated every month before each dose, and continuing for up to six months after the last dose.^{1,15}

Glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. Glatiramer acetate is a mixture of synthetic polypeptides, made through a chemical synthesis from four amino acids. The mixture is antigenically similar to myelin basic protein, a component of the myelin sheath of nerves. Experimental models suggest glatiramer may bind to major histocompatibility complex molecules and compete with various myelin antigens for their presentation to T cells. In addition, glatiramer is a potent inducer of specific T helper 2 type suppressor cells that migrate to the brain and lead to bystander suppression; these cells also express anti-inflammatory cytokines.^{4,5,15} In April 2015, the FDA approved the first generic disease-modifying therapy for MS: Glatopa[®] 20 mg/mL. Glatopa[®] approval utilized the Abbreviated New Drug Application (ANDA) regulatory pathway, which is the pathway used for development and FDA approval of generic drugs. Glatopa[®] is fully substitutable for Copaxone[®] 20 mg/mL for relapsing-forms of MS.^{5,14,19}

Natalizumab is a recombinant monoclonal antibody directed against alpha-4 integrins. The formation of inflammatory lesions in patients with MS may involve lymphocytes and monocytes that gain access to the brain parenchyma from the circulation by first adhering to vascular endothelial cells. Alpha-4 integrin is expressed on the surface of inflammatory lymphocytes and monocytes and may play a critical role in their adhesion to the vascular endothelium. Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing treatment with natalizumab, physicians should consider whether the expected benefit is sufficient to offset this risk. Natalizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH[®] Prescribing Program because of the risk of PML.^{9,15}

IFNs are pleiotropic molecules with a wide range of proliferative, apoptotic, antiviral, and complex immunoregulatory activities.^{6-8,10,11,15} Although first attempts to use IFNs as therapeutic agents in MS were based

on their antiviral effect, more recent attention has focused on their direct effect on the blood-brain barrier and their immunomodulatory and antiproliferative effects.²⁰ These are the oldest treatments for RRMS, the first being approved in 1993.¹⁵

Oral products include dimethyl fumarate (Tecfidera[®]), fingolimod (Gilenya[®]), and teriflunomide (Aubagio[®]). Dimethyl fumarate may have neuroprotective and immunomodulatory properties, although the mechanism by which it exerts its therapeutic effect in multiple sclerosis is unknown. The mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system.^{2,15} Fingolimod is sphingosine analogue that modulates the sphingosine-1-phosphate receptor and thereby alters lymphocyte migration, resulting in sequestration of lymphocytes in lymph nodes. Initiation of fingolimod treatment results in a decrease in heart rate. The first dose of fingolimod should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. In order to assess patient response to the first dose of fingolimod, observe all patients for six hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. In all patients, obtain an electrocardiogram prior to dosing, and at the end of the observation period.^{3,15} Teriflunomide is the active metabolite of leflunomide that inhibits pyrimidine biosynthesis and disrupts the interaction of T cells with antigen presenting cells. The exact mechanism by which teriflunomide exerts its therapeutic effect is unknown but may involve a reduction in the number of activated lymphocytes in the central nervous system. Teriflunomide carries a boxed warning for the risks of hepatotoxicity and teratogenicity. The manufacturer recommends obtaining baseline transaminase and bilirubin levels before starting treatment with teriflunomide, and to monitor ALT levels monthly for at least six months once treatment is started.^{12,15}

The immunomodulatory agents used to treat multiple sclerosis included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Glatiramer acetate 20 mg/mL is available in a generic formulation. This is the first review of this class.

Table 1. Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Daclizumab	injection	Zinbryta [®]	none
Dimethyl fumarate	capsule	Tecfidera [®]	none
Fingolimod	capsule	Gilenya [®]	none
Glatiramer acetate	injection	Copaxone ^{®*} , Glatopa ^{®†}	none
Interferon β-1a	injection	Avonex [®] , Avonex Pen [®] , Rebif [®] , Rebif Rebidose [®]	none
Interferon β-1b	injection	Betaseron [®] , Extavia [®]	none
Natalizumab	injection	Tysabri [®]	none
Peginterferon β-1a	injection	Plegridy [®]	none
Teriflunomide	tablet	Aubagio [®]	none

PDL=Preferred Drug List

*Generic available in at least one dosage form or strength.

†Glatopa[®] is a generic equivalent of Copaxone[®] 20 mg.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Immunomodulatory Agents used to treat Multiple Sclerosis

Clinical Guideline	Recommendation(s)
Association of British Neurologists: Revised Guidelines for Prescribing in Disease-Modifying Treatments for Multiple Sclerosis (2015) ¹⁷	<p>General Statements</p> <ul style="list-style-type: none"> All of the licensed disease-modifying treatments for multiple sclerosis (MS)- β- interferons, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, natalizumab and alemtuzumab- reduce relapse rate and magnetic resonance imaging (MRI) lesion accumulation in relapsing–remitting MS, to varying extents. Reducing relapse rate and MRI lesion accumulation data shows only a weak correlation between long-term disability and relapse frequency.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • There is a consensus that none of the currently available disease-modifying therapies significantly modifies progressively increasing disability that is unrelated to relapses (progressive non-relapsing MS). • Long-term therapy with disease-modifying agents has not established the following: <ul style="list-style-type: none"> ○ Reduces the accumulation of disability by whatever mechanism. ○ Prevents or slows entry to the secondary progressive stage of the disease. • Immunotherapies appear particularly helpful when given early to people with active relapsing–remitting disease, before there is fixed disability or secondary progression. • Disease-modifying treatment should be started and supervised by an MS specialist neurologist. • When considering potential disease-modifying treatment options, it is important that patients and neurologists fully appreciate the risk and benefit of drugs, and of leaving the disease untreated. • Provide patients accurate information: <ul style="list-style-type: none"> ○ Expectations of treatment, including the evidence that disease-modifying treatment efficacy can be only partial, moderate and not curative. ○ Risk as well as expected benefit of treatment. ○ Monitoring requirements of treatment. • Discuss work, family and other factors that are personally important to them and take their views into account when making the treatment selection. <p>Initial Treatment Recommendations: Relapsing–Remitting MS (RRMS)</p> <ul style="list-style-type: none"> • Licensed agents are broadly divided into two classes: <ul style="list-style-type: none"> ○ Drugs of moderate efficacy (Category 1): <ul style="list-style-type: none"> ▪ β-interferons (including pegylated β-interferon) ▪ glatiramer acetate ▪ teriflunomide ▪ dimethyl fumarate ▪ fingolimod ○ Drugs of high efficacy (Category 2): <ul style="list-style-type: none"> ▪ alemtuzumab ▪ natalizumab • Consider starting treatment with disease-modifying agents in patients with “active” RRMS • Activity may be established on radiological/clinical grounds: • Active RRMS: <ul style="list-style-type: none"> ○ Consider treatment in patients: <ul style="list-style-type: none"> ▪ who have had two or more clinical relapses in the previous two years ▪ who have had a single recent relapse and/or on radiological grounds, including both patients newly diagnosed according to the 2010 ‘MacDonald criteria’ ▪ with established disease who develop new MRI lesions without clinical relapse ○ Usually start with a Category 1 drug. <ul style="list-style-type: none"> ▪ Dimethyl fumarate and fingolimod appear to be most effective. β-Interferon, teriflunomide and glatiramer acetate appear to be similar (broadly), but are probably a little less effective. ▪ Dimethyl fumarate and fingolimod have the additional benefit of being an oral agent. ▪ β-interferons and glatiramer acetate have been used

Clinical Guideline	Recommendation(s)
	<p>extensively for decades in MS, and there is a wealth of clinical experience confirming their general safety.</p> <ul style="list-style-type: none"> • More Active RRMS <ul style="list-style-type: none"> ○ Patients may be classified as having more active MS by frequent clinical relapses and/or MRI activity either when untreated or while on a Category 1 drug. ○ The formal criteria for high-disease activity despite interferon-β or glatiramer requires one relapse in the previous year on interferon-β and either: ≥1 gadolinium-enhancing MRI lesions or at least nine T2-hyperintensive lesions on cranial MRI ○ It is recommended to begin a Category 2 agent in patients with high disease activity: natalizumab or alemtuzumab. <ul style="list-style-type: none"> ▪ Indirect comparison suggests that alemtuzumab and natalizumab have similar efficacy. ▪ Appropriate where individuals and their neurologists are most concerned to achieve high efficacy, despite the more complex safety profile compared to Category 1 drugs. ○ It may be appropriate to change from one Category 1 agent to another Category 1 agent: <ul style="list-style-type: none"> ▪ Patients with infrequent or occasional minor relapses ▪ Patient may be risk-averse to safety profile of Category 2 agents ▪ Consider the increased potency of fingolimod and dimethyl fumarate <p><u>People aged under 18 years</u></p> <ul style="list-style-type: none"> • Minors aged between 16 and 18 years should be treated according to the above guidelines. • Children with MS aged <16 should be treated in specialist clinics, preferably under a combined team including adult and paediatric neurologists with a particular interest in MS. <p><u>Primary or secondary progressive MS</u></p> <ul style="list-style-type: none"> • None of the current disease-modifying treatments is recommended in non-relapsing secondary progressive MS or in primary progressive MS. • Some people with relapsing secondary progressive MS, whose relapses are their main cause of increasing disability, may benefit from disease-modifying treatment. <p><u>Recommendations for Stopping Disease-Modifying Treatment</u></p> <ul style="list-style-type: none"> • Mandatory stopping criteria that applies to all patients is not appropriate • The difficulty of stopping treatment in people with progressive disease is compounded by the absence of alternative options for disease modification • Clinicians should consider stopping disease-modifying treatment in the following scenarios: <ul style="list-style-type: none"> ○ Significant side effects specific to any individual agent ○ Development of non-relapsing secondary progressive MS ○ Pregnancy • If significant side effects develop to a specific agent, that agent should be discontinued and an alternative should be considered • Disease-modifying treatments should normally be stopped during pregnancy, as stated in the summary of product characteristics. Known risks and available information vary by agent. <ul style="list-style-type: none"> ○ Given the increased risk of relapse in the puerperium, treatment should be restarted early after delivery, depending on discussions concerning breast feeding.

Clinical Guideline	Recommendation(s)
<p>American Academy of Neurology/ Multiple Sclerosis Council for Clinical Practice Guidelines: Disease Modifying Therapies in Multiple Sclerosis (2002)¹⁸</p> <p>Reaffirmed July 2008</p>	<ul style="list-style-type: none"> • No one agent is recommended over another, but glucocorticoids, interferon beta and glatiramer acetate have the strongest recommendations for use in relapsing forms of multiple sclerosis (MS). <p><u>Glucocorticoids</u></p> <ul style="list-style-type: none"> • Glucocorticoids have been demonstrated to provide short-term benefits on the speed of functional recovery in patients with acute attacks of MS. Consider glucocorticoids for treatment of any patient with an acute attack of MS (Type A recommendation). • There are no apparent long-term benefits of glucocorticoids on MS (Type B recommendation). • Clinical benefits of glucocorticoids are not influenced by particular glucocorticoid, route of administration or dosage (Type C recommendation). • Regular pulse glucocorticoids may be useful in the long-term management of relapsing-remitting MS (RRMS) (Type C recommendation). <p><u>Interferon beta (IFNβ)</u></p> <ul style="list-style-type: none"> • IFNβ has been shown to reduce the attack rate in patients with MS or with clinically isolated syndromes at high risk for developing MS (Type A recommendation). • IFNβ treatment produces a beneficial effect on MRI measures of disease severity and probably also slows disability progression (Type B recommendation). • Consider IFNβ treatment for any patient at high risk of developing MS or any patient with RRMS or secondary-progressive MS (SPMS) still experiencing relapses (Type A recommendation). • It is probable that there is a dose-response curve associated with the use of IFNβ for MS (Type B recommendation). • The route of administration of IFNβ is probably not of clinical importance with regard to efficacy, although the side-effect profile does differ (Type B recommendation). • IFNβ treatment is associated with the production of neutralizing antibodies, but the rate of production is probably less with IFNβ-1a than IFNβ-1b (Type B recommendation). Their presence may be associated with a reduction in clinical effectiveness of IFNβ treatment (Type C recommendation). <p><u>Glatiramer acetate</u></p> <ul style="list-style-type: none"> • Glatiramer acetate has been shown to reduce attack rates, produce a beneficial effect on MRI measures of disease severity and possibly slow disability progression in RRMS. • Consider glatiramer acetate in any patient with RRMS (Type A recommendation). <p><u>Cyclophosphamide</u></p> <ul style="list-style-type: none"> • Pulse cyclophosphamide treatment does not alter the course of progressive MS (Type B recommendation). • It is possible that younger patients with progressive MS may derive some benefit from pulse plus booster cyclophosphamide (Type U recommendation). <p><u>Methotrexate</u></p> <ul style="list-style-type: none"> • It is possible that methotrexate favorably alters disease course in progressive MS (Type C recommendation). <p><u>Azathioprine</u></p> <ul style="list-style-type: none"> • Azathioprine may reduce relapse rate in MS (Type C recommendation).

Clinical Guideline	Recommendation(s)
	<p><u>Cladribine</u></p> <ul style="list-style-type: none"> • Cladribine reduces gadolinium enhancement in relapsing and progressive MS, but does not favorably alter disease course (Type C recommendation). <p><u>Cyclosporine</u></p> <ul style="list-style-type: none"> • It is possible that cyclosporine provides some therapeutic benefits in progressive MS (Type C recommendation). • Cyclosporine is not recommended due to frequency of adverse events and small magnitude of potential benefit (Type B recommendation). <p><u>Mitoxantrone</u></p> <ul style="list-style-type: none"> • Mitoxantrone probably reduces attack rate in relapsing MS, but its potential toxicity may outweigh benefits early in disease course (Type B recommendation). <p><u>Intravenous immunoglobulin</u></p> <ul style="list-style-type: none"> • It is only possible that intravenous immunoglobulin reduces attack rate in RRMS (Type C recommendation). • Intravenous immunoglobulin is of little benefit in slowing disease progression (Type C recommendation). <p><u>Plasma exchange</u></p> <ul style="list-style-type: none"> • Plasma exchange may be helpful in the treatment of severe acute episodes of demyelination in previously nondisabled individuals (Type C recommendation).
<p>National Institute for Clinical Excellence: Fingolimod for the Treatment Highly Active Relapsing-Remitting Multiple Sclerosis (2012)²¹</p>	<ul style="list-style-type: none"> • Fingolimod is recommended as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if: <ul style="list-style-type: none"> ○ They have an unchanged or increased relapse rate or ongoing severe relapses compared to the previous year despite treatment with beta interferon, and ○ The manufacturer provides fingolimod with the discount agreed as a part of the patient access scheme • People currently receiving fingolimod whose disease does not meet the above criteria should continue treatment unless they or their clinician feels it is appropriate to stop
<p>National Institute for Clinical Excellence: Teriflunomide for the Treating Relapsing-Remitting Multiple Sclerosis (2014)²²</p>	<ul style="list-style-type: none"> • Teriflunomide is recommended as an option for treating adults with active relapsing–remitting multiple sclerosis (normally defined as two clinically significant relapses in the previous two years), only if: <ul style="list-style-type: none"> ○ They do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis AND ○ The manufacturer provides teriflunomide with the discount agreed in the patient access scheme.
<p>National Institute for Health Care and Excellence: Multiple Sclerosis in Adults: Management (2014)²³</p>	<p><u>Vaccinations</u></p> <ul style="list-style-type: none"> • Live vaccinations may be contraindicated in people with MS who are being treated with disease-modifying therapies. • Discuss the possible benefits of flu vaccination for patients with MS. • Discuss the possible risk of relapse after flu vaccination if the patient has relapsing–remitting MS. • Offer flu vaccinations to people with MS in accordance with national guidelines. <p><u>MS symptom management and rehabilitation</u></p> <ul style="list-style-type: none"> • <u>Fatigue</u> <ul style="list-style-type: none"> ○ Assess and offer treatment to people with MS who have fatigue. ○ Explain precipitating factors (e.g. heat, overexertion, stress or may be

Clinical Guideline	Recommendation(s)
	<p>related to the time of day).</p> <ul style="list-style-type: none"> ○ Offer amantadine to treat fatigue in people with MS. ○ Consider mindfulness-based training, cognitive behavioral therapy or fatigue management. ○ Advise people that aerobic, balance and stretching exercises including yoga may be helpful in treating MS-related fatigue. ○ Do not use vitamin B₁₂ injections to treat fatigue. ○ Consider a comprehensive programme of aerobic and moderate progressive resistance activity combined with cognitive behavioral techniques for fatigue in people with MS with moderately impaired mobility <ul style="list-style-type: none"> ● Spasticity <ul style="list-style-type: none"> ○ Offer treatment for factors that may aggravate spasticity (e.g. constipation, urinary tract or other infections, inappropriately fitted mobility aids, pressure ulcers, posture and pain). ○ Encourage management of their own spasticity symptoms. ○ Ensure that the person with MS: <ul style="list-style-type: none"> ▪ Has tried the drug at an optimal dose, or the maximum dose they can tolerate ▪ Stops the drug if there is no benefit at the maximum tolerated dose ▪ Has their drug treatment reviewed at least annually once the optimal dose has been reached ○ Consider baclofen or gabapentin first-line drug <ul style="list-style-type: none"> ▪ Consider switching to the other agent if the first cannot be tolerated. ○ Consider a combination of baclofen and gabapentin for people with MS if: individual drugs do not provide adequate relief or side effects from individual drugs prevent the dose being increased. ○ Consider tizanidine or dantrolene second-line. ○ Consider benzodiazepines third-line option; be aware of their potential benefit in treating nocturnal spasms. ○ Do not offer Sativex to treat spasticity in people with MS because it is not a cost effective treatment. ○ If spasticity cannot be managed with any of the above pharmacological treatments, refer the person to specialist spasticity services. ● Oscillopsia <ul style="list-style-type: none"> ○ Consider gabapentin first-line ○ Consider memantine as the second-line treatment ○ Refer the person with MS for specialist advice if there is no improvement of oscillopsia after treatment with gabapentin and memantine or side effects prevent continued use. ● Emotional lability <ul style="list-style-type: none"> ○ Consider amitriptyline to treat emotional lability ● Pain <ul style="list-style-type: none"> ○ Neuropathic pain should be treated according to clinical guidelines ○ Musculoskeletal pain is common and should be assessed; offer treatment to the person and refer them as appropriate. <p><u>Relapse and exacerbation</u></p> <ul style="list-style-type: none"> ● Treating acute relapse of MS with steroids <ul style="list-style-type: none"> ○ Oral methylprednisolone 0.5 g daily for five days ○ Consider intravenous methylprednisolone 1 g daily for three to five

Clinical Guideline	Recommendation(s)
	<p>days as an alternative for people with MS:</p> <ul style="list-style-type: none"> ▪ in whom oral steroids have failed or not been tolerated; or ▪ who need admitting to hospital for a severe relapse or monitoring of medical or psychological conditions such as diabetes or depression <ul style="list-style-type: none"> ○ Do not prescribe steroids at lower doses than methylprednisolone 0.5 g daily for five days to treat an acute relapse of MS. ○ Do not give people with MS a supply of steroids to self-administer at home for future relapses. <p>Other treatments</p> <ul style="list-style-type: none"> • Do not offer vitamin D solely for the purpose of treating MS. • Do not offer omega-3 or omega-6 fatty acid compounds to treat MS.
<p>Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology: Neutralizing Antibody to Interferon β: Assessment of Their Clinical and Radiographic Impact: an Evidence Report (2007)²⁴</p> <p>Reaffirmed January 2016</p>	<ul style="list-style-type: none"> • It is probable that the presence of neutralizing antibodies (NAbs), especially in persistently high titers, is associated with a reduction in the radiographic and clinical effectiveness of interferon β (IFNβ) treatment. • It is probable that the rate of NAb production is less with IFNβ-1a treatment compared to IFNβ-1b treatment. However, the magnitude and persistence of any difference in between these forms of IFNβ is difficult to determine. • It is probable that the prevalence of NAbs to IFNβ is affected by ≥ 1 of the following: formulation, route of administration, dose and/or frequency of administration.
<p>National Clinical Advisory Board of the National Multiple Sclerosis Society: Multiple Sclerosis Disease Management Consensus Statement (2008)²⁵</p>	<ul style="list-style-type: none"> • Initiation of treatment with an interferon β (IFNβ) product or glatiramer acetate (GA) should be considered as soon as possible following a definite diagnosis of multiple sclerosis (MS) with active, relapsing disease. • Initiation of treatment with an IFNβ product or GA may also be considered for select patients with a first attack who are at high risk of MS. • Natalizumab is generally recommended by the Food and Drug Administration (FDA) for patients who have had an inadequate response to, or are unable to tolerate, other MS therapies. • Mitoxantrone may be considered for selected relapsing patients with worsening disease or patients with secondary progressive multiple sclerosis (SPMS) who are worsening, whether or not relapses are occurring. • Access to medication should not be limited by the frequency of relapses, age or level of disability. • Treatment should not be discontinued while insurers evaluate for continuing coverage of treatment. • Therapy should be continued indefinitely, except for the following circumstances: clear lack of benefit, intolerable side effects or availability of better therapy. • The most appropriate agent should be selected on an individual basis. • All FDA-approved agents should be included in formularies and covered so that the most appropriate agent for an individual can be utilized; failure to do so is unethical and discriminatory. • Transition from one disease-modifying agent to another should occur only for medically appropriate reasons. • No therapy has been approved for use by women who are trying to become

Clinical Guideline	Recommendation(s)
<p>The Multiple Sclerosis Coalition: The Use of Disease-Modifying Therapies in Multiple Sclerosis (2014)²⁶ Updated July 2016</p>	<p>pregnant, are pregnant or are nursing mothers.</p> <p>Treatment considerations</p> <ul style="list-style-type: none"> • Initiation of treatment with an FDA-approved disease-modifying therapy is recommended: <ul style="list-style-type: none"> ○ As soon as possible following a diagnosis of relapsing disease, regardless of the person’s age. ○ For individuals with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded. ○ For individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity. • Treatment with a given disease-modifying medication should be continued indefinitely unless any of the following occur (in which case an alternative disease-modifying therapy should be considered): <ul style="list-style-type: none"> ○ Sub-optimal treatment response as determined by the individual and his or her treating clinician. ○ Intolerable side effects. ○ Inadequate adherence to the treatment regimen. ○ Availability of a more appropriate treatment option. • Movement from one disease-modifying therapy to another should occur only for medically appropriate reasons as determined by the treating clinician and patient. • When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit. • The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed collaboratively by the individual and his or her treating clinician.
<p>National Institute for Health and Clinical Excellence: Natalizumab for the Treatment of Adults With High Active Relapsing-Remitting Multiple Sclerosis (Appraisal) (2007)²⁷</p>	<ul style="list-style-type: none"> • Natalizumab is recommended as an option for the treatment only of rapidly evolving severe relapse-remitting multiple sclerosis (RRMS), defined as two or more disabling relapses in one year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared to a previous MRI. • Patients currently receiving natalizumab, but for whom treatment would not have been recommended based on the above bullet, should have the option to continue therapy until they and their clinicians consider it appropriate to stop. • Natalizumab also has marketing authorization as a single disease modifying therapy in highly active RRMS for patients with high disease activity despite treatment with interferon β (IFNβ). This group of patients is defined as patients who have failed to respond to a full and adequate course of IFNβ. These patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial MRI or at least one gadolinium-enhancing lesion. This group of patients is referred to as the “suboptimal therapy group.” • Natalizumab has been associated with an increased risk of progressive multifocal leukoencephalopathy. Use may also be associated with infections, urticaria, headache, dizziness, vomiting, nausea, arthralgia, infusion reactions and hypersensitivity reactions.

III. Indications

The FDA-approved indications for immunomodulatory agents used to treat multiple sclerosis are noted in Table 3.

Table 3. FDA-Approved Indications for the Immunomodulatory Agents used to treat Multiple Sclerosis¹⁻¹⁴

Generic Name	Treatment of patients with relapsing forms of multiple sclerosis
--------------	--

Generic Name	Treatment of patients with relapsing forms of multiple sclerosis
Daclizumab	✓*
Dimethyl fumarate	✓
Fingolimod	✓†
Glatiramer acetate	✓
Interferon β-1a	✓†
Interferon β-1b	✓‡
Natalizumab§	✓
Peginterferon β-1a	✓
Teriflunomide	✓

*Because of its safety profile, the use of daclizumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

†Treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.

‡Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

§Tysabri® is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of TNF-α. This indication is outside the scope of this review.

IV. Pharmacokinetics

The pharmacokinetic parameters of the immunomodulatory agents used to treat multiple sclerosis are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Immunomodulatory Agents used to treat Multiple Sclerosis¹³

Generic Name(s)	Bioavailability	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Daclizumab	90	Not reported	Catabolism to peptides and amino acids	Renal (% not reported)	21 days
Dimethyl fumarate	Not reported	27 to 45	GI tract, blood, and tissues (extensive)	Renal (16), Feces (1), Respiratory (60)	1 hour
Fingolimod	93	>99.7	Liver (extensive)	Renal (81), Feces (<2.5)	6 to 9 days
Glatiramer acetate	Not reported	Not reported	Local hydrolysis	Not reported	Not reported
Interferon β-1a	Not reported	Not reported	Not reported	Not reported	IM: 19 hours SQ: 69 hours
Interferon β-1b	50	Not reported	Not reported	Renal (minimal)	Not reported
Natalizumab	Not reported	Not reported	Not reported	Not reported	11 days
Peginterferon β-1a	Not reported	Not reported	Catabolism	Renal (extensive)	78 hours
Teriflunomide	Not reported	>99	Hydrolysis	Renal (22.6), Feces (37.5)	18 to 19 days

V. Drug Interactions

Major drug interactions with the immunomodulatory agents used to treat multiple sclerosis are listed in Table 5.

Due to their potential to cause hepatic injury, patients must be monitored when interferon β (IFNβ) is administered in combination with another agent that can cause hepatic injury, or when new agents are added to a regimen of a patient already receiving IFNβ.¹³⁻¹⁴

Table 5. Major Drug Interactions with the Immunomodulatory Agents used to treat Multiple Sclerosis¹⁻¹³

Generic Name(s)	Interaction	Mechanism
Biological response modifiers (interferon β , fingolimod, teriflunomide)	Live vaccines	Concurrent use of may result in an increased risk of secondary transmission of infection and reduced effectiveness of immunization.
Fingolimod	Class Ia antiarrhythmic agents (flecainide, mexiletine, procainamide)	Concurrent use of fingolimod and Class Ia antiarrhythmic agents may result in increased risk of developing bradycardia or heart block.
Fingolimod	Class III antiarrhythmic agents (amiodarone, dronedarone, sotalol)	Concurrent use of fingolimod and Class III antiarrhythmic agents may result in increased risk of developing bradycardia or heart block.
Fingolimod	Drugs that slow heart rate (beta-blockers, diltiazem, verapamil, digoxin)	Initiation of fingolimod is associated with slowing of the heart rate and experience is limited when using drugs that slow heart rate. If patients cannot be switched, they should have overnight electrocardiogram monitoring after the first dose.
Fingolimod	Ketoconazole	Concomitant administration may result in an increase in fingolimod exposure and a greater risk of adverse events.
Teriflunomide	Breast Cancer Resistant Protein (BCRP) inhibitors (cyclosporine, eltrombopag, gefitinib)	BCRP inhibitors may increase exposure to teriflunomide and increase risk of adverse events.
Teriflunomide	CYP2C8 substrates (repaglinide, paclitaxel, pioglitazone)	Teriflunomide may be an inhibitor of CYP2C8, resulting in increased exposure of CYP2C8 substrates. Patient monitoring is recommended.
Teriflunomide	CYP1A2 substrates (duloxetine, alosetron, theophylline, tizanidine)	Teriflunomide may be a weak inducer of CYP1A2, resulting in reduced exposure of CYP1A2 substrates. Monitor for decreased efficacy of CYP1A2 substrates.
Teriflunomide	Oral contraceptives	Teriflunomide may increase exposure and risk of estrogen and progestin-related adverse effects. Consider type and dose of oral contraceptive.

VI. Adverse Drug Events

The most common adverse drug events reported with the immunomodulatory agents used to treat multiple sclerosis are listed in Table 6. Boxed warnings are in Tables 7 through 9.

Table 6. Adverse Drug Events (%) Reported with the Immunomodulatory Agents used to treat Multiple Sclerosis¹⁴

Adverse Event	Daclizumab	Dimethyl Fumarate	Fingolimod	Glatiramer Acetate	Interferon β -1b*	Interferon β -1a (Rebif®)	Interferon β -1a (Extavia®)	Natalizumab	Peginterferon β -1a	Terifunomide
Cardiovascular										
Atrioventricular block			0.1%							
Bradycardia			4							
Chest pain				13	9	6 to 8	5	5		
Hypertension			6		6					4
Palpitations				9						2 to 3
Tachycardia				5						
Vasodilatation				20			2			
Central Nervous System										
Burning sensation										2 to 3
Convulsions						4 to 5				
Dizziness			7				14			
Fatigue						33 to 41		27		
Fever					31					
Headache			25		50	65 to 70	58	38	44	19 to 22
Malaise					6	4 to 5				
Migraine			5	4			5			
Incoordination					17	4 to 5				
Insomnia					21					
Paresthesia			5							9 to 10
Pyrexia				6					45	
Sciatica										1 to 3
Somnolence						4 to 5		2		
Speech disorder				2						
Syncope				3						
Tremor				4						
Vertigo							6			
Weight decreased							2			2 to 3

Adverse Event	Daclizumab	Dimethyl Fumarate	Fingolimod	Glatiramer Acetate	Interferon β -1b*	Interferon β -1a (Rebif®)	Interferon β -1a (Extavia®)	Natalizumab	Peginterferon β -1a	Teriflunomide
Weight increased	-	-	-	-	-	-	-	2	-	-
Endocrine										
Thyroid disorder	-	-	-	-	-	4 to 6	-	-	-	-
Gastrointestinal										
Abdominal pain	-	18	-	-	16	20 to 22	8	11	-	5 to 6
Diarrhea	-	14	12	-	-	-	-	10	-	15 to 18
Dry mouth	-	-	-	-	-	1 to 5	-	-	-	-
Dyspepsia	-	5	-	-	-	-	-	-	-	-
Distension	-	-	-	-	-	-	-	-	-	1 to 2
Nausea	-	12	-	15	-	-	23	-	9	9 to 14
Toothache	-	-	-	-	-	-	-	-	-	4
Vomiting	-	9	-	7	-	-	-	-	5	-
Hematologic										
Anemia	-	-	-	-	-	3 to 5	4	-	-	-
Hypertriglyceridemia	-	-	3	-	-	-	-	-	-	-
Injection site ecchymosis	-	-	-	-	-	-	6	-	-	-
Leukopenia	-	-	3	-	13	28 to 36	-	-	-	1 to 2
Lymphadenopathy	5	-	-	7	6	11 to 12	-	-	-	-
Lymphomas	-	-	✓	-	-	-	-	-	-	-
Lymphopenia	-	2	4	-	86	-	-	-	-	1 to 3
Neutropenia	-	-	-	-	13	-	-	-	-	2 to 4
Thrombocytopenia	-	-	-	-	-	2 to 8	-	-	-	-
Hepatic										
Abnormal hepatic function	-	-	-	-	-	4 to 9	-	5	-	-
Alanine aminotransferase liver enzymes increased	5	-	14	-	12	20 to 27	-	-	-	12 to 14
Aspartate aminotransferase liver enzymes increased	5	4	14	-	4	10 to 17	-	-	-	2 to 3
Bilirubinemia	-	-	-	-	-	2 to 3	-	-	-	-
Gamma-glutamyl transpeptidase liver enzymes increased	-	-	5	-	-	-	-	-	-	-
Gamma-glutamyltransferase increased	-	-	-	-	-	-	-	-	-	3 to 5
Infections										
Bronchitis	-	-	-	-	-	-	-	-	-	5 to 8

Adverse Event	Daclizumab	Dimethyl Fumarate	Fingolimod	Glatiramer Acetate	Interferon β -1b*	Interferon β -1a (Rebif®)	Interferon β -1a (Extavia®)	Natalizumab	Peginterferon β -1a	Teriflunomide
Cystitis										2 to 4
Fungal infections										
Gastroenteritis			5	6				11		2 to 4
Herpes viral infection			9					8		2 to 4
Influenza-like symptoms	9		13	14	57	56 to 59	49		47	9 to 12
Lower respiratory tract infection								17		
Nasopharyngitis	25									
Sinusitis										4 to 6
Tinea infections			4							
Tonsillitis								7		
Tooth infections								9		
Upper respiratory tract infection	9 to 17						14			9
Vaginal candidiasis				4				10		
Musculoskeletal										
Arthralgia or myalgia				24	23	25	9 to 29	19	11 to 19	3 to 4
Asthenia			3	41	53		24			
Back pain			12	12		23 to 25				
Chills				3	21				17	
Hypertonia				22	40	6 to 7				
Pain				28	42		23	16		4 to 5
Rigors								3		
Skeletal pain						10 to 15				
Ophthalmic										
Abnormal vision						7 to 13				
Blurred vision			4							3
Conjunctivitis										1 to 3
Diplopia				3						
Eye disorder				3			4			
Eye pain			3							
Xerophthalmia						1 to 3				
Psychiatric										
Anxiety				13						3 to 4
Depression	7		8				18	19		
Nervousness				2						

Adverse Event	Daclizumab	Dimethyl Fumarate	Fingolimod	Glatiramer Acetate	Interferon β -1b*	Interferon β -1a (Rebif®)	Interferon β -1a (Extavia®)	Natalizumab	Peginterferon β -1a	Teriflunomide
Respiratory										
Bronchitis	7		8	6			8			
Cough			10	6						
Dyspnea			8	14	6					
Laryngospasm				2						
Seasonal allergy								3		2 to 3
Sinusitis			7	7			14			
Throat Pain	8									
Skin and Subcutaneous Tissue										
Acne										1 to 3
Alopecia			4				4			10 to 13
Dermatitis	3 to 9							7		
Eczema	5		3							
Edema				8						
Erythema		5								
Flushing		40								
General skin disorder	18 to 37									
Hyperhidrosis				7						
Hypersensitivity				3				5		
Hyperthermia									4	
Injection site necrosis					4	1 to 3				
Injection site reactions				4 to 64	78	89 to 92	6 to 8		62	
Pruritus		8	3	5				4	13	3 to 4
Psoriasis	2									
Rash	7 to 11	8		19	21	4 to 7		12		
Skin disorder				3	10					
Urticaria				3						
Urogenital										
Albumin urine present		6								
Amenorrhea								2		
Blood in urine										
Dysmenorrhea								3		
Impotence					8					
Irregular menstruation								5		

Adverse Event	Daclizumab	Dimethyl Fumarate	Fingolimod	Glatiramer Acetate	Interferon β -1b*	Interferon β -1a (Rebif®)	Interferon β -1a (Extavia®)	Natalizumab	Peginterferon β -1a	Teriflunomide
Metrorrhagia					9					
Micturition urgency				5		2 to 7		9		
Ovarian cyst								2		
Urinary incontinence						2 to 4		4		
Urinary tract infection							17	21		
Urine constituents abnormal							3			

✓ Percent not specified.

- Event not reported.

* Betaseron®, Extavia®

§ Initiation of fingolimod treatment has resulted in transient atrioventricular (AV) conduction delays. In clinical trials, first degree AV block (prolonged PR interval on electrocardiogram) following the first dose was reported in 0.1% of patients receiving fingolimod 0.5 mg, but in no patient receiving placebo. Second degree AV block following the first dose was also identified in 0.1% of patients receiving fingolimod 0.5 mg but in no patient receiving placebo.

|| Cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) were reported in premarketing clinical trials in multiple sclerosis patients receiving fingolimod at, or above, the recommended dose of 0.5 mg. Based on the small number of cases and short duration of exposure, the relationship to fingolimod remains uncertain.

Table 7. Black Box Warning for Zinbryta® (Daclizumab)¹

WARNING
<p>Hepatic Injury Including Autoimmune Hepatitis</p> <p>Daclizumab can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. In clinical trials, one patient died due to autoimmune hepatitis. Liver injury, including autoimmune hepatitis, can occur at any time during treatment with daclizumab, with cases reported up to four months after the last dose of daclizumab.</p> <p>Daclizumab is contraindicated in patients with pre-existing hepatic disease or hepatic impairment. Prior to starting daclizumab, obtain serum transaminases (ALT and AST) and bilirubin levels. Test transaminase levels and total bilirubin monthly and assess before the next dose of daclizumab. Follow transaminase levels and total bilirubin monthly for six months after the last dose of daclizumab.</p> <p>In case of elevation in transaminases or total bilirubin, treatment interruption or discontinuation may be required.</p> <p>Other Immune-Mediated Disorders</p> <p>In addition to autoimmune hepatitis, immune-mediated disorders such as skin reactions, lymphadenopathy, and non-infectious colitis can occur in patients treated with daclizumab. Overall, serious immune-mediated conditions were observed in 5% of patients treated with daclizumab.</p> <p>If a patient develops a serious immune-mediated disorder, consider stopping daclizumab and refer the patient to a specialist to ensure comprehensive diagnostic evaluation and appropriate treatment.</p>

WARNING

Some patients required systemic corticosteroids or other immunosuppressant treatment for autoimmune hepatitis or other immune-mediated disorders and continued this treatment after the last dose of daclizumab.

Because of the risks of hepatic injury, including autoimmune hepatitis, and other immune-mediated disorders, daclizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the daclizumab REMS Program.

Table 8. Black Box Warning for Tysabri® (Natalizumab)⁹

WARNING

Progressive Multifocal Leukoencephalopathy

Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Risk factors for the development of PML include duration of therapy, prior use of immunosuppressants, and presence of anti-JCV antibodies. These factors should be considered in the context of expected benefit when initiating and continuing treatment with Tysabri.

- Healthcare professionals should monitor patients on Tysabri for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.
- Because of the risk of PML, Tysabri is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH Prescribing Program.

Table 9. Black Box Warning for Aubagio® (Teriflunomide)¹²

WARNING

Hepatotoxicity

Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. Obtain transaminase and bilirubin levels within six months before initiation of teriflunomide and monitor alanine aminotransferase levels at least monthly for six months. If drug induced liver injury is suspected, discontinue teriflunomide and start accelerated elimination procedure.

Risk of Teratogenicity

Based on animal data, teriflunomide may cause major birth defects if used during pregnancy. Teriflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during teriflunomide treatment.

VII. Dosing and Administration

The usual dosing regimens for the immunomodulatory agents used to treat multiple sclerosis are listed in Table 10.

Table 10. Usual Dosing Regimens for the Immunomodulatory Agents used to treat Multiple Sclerosis¹⁻¹⁴

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Daclizumab	Treatment of patients with relapsing forms of multiple sclerosis: Prefilled syringe: inject 150 mg SC (thigh, abdomen, back of upper arm) once a month	Safety and efficacy in children <17 years of age have not been established.	Injection: 150 mg/mL
Dimethyl fumarate	Treatment of patients with relapsing forms of multiple sclerosis: Delayed-release capsule: initial, 120 mg BID for seven days; maintenance, 240 mg BID	Safety and efficacy in children <18 years of age have not been established.	Delayed-release capsule: 120 mg 240 mg
Fingolimod	Treatment of patients with relapsing forms of multiple sclerosis: Capsule: 0.5 mg orally once daily [First dose monitoring: The first dose of fingolimod should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. In order to assess patient response to the first dose of fingolimod, observe all patients for six hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Obtain in all patients an electrocardiogram prior to dosing, and at the end of the observation period.]	Safety and efficacy in children <18 years of age have not been established.	Capsule: 0.5 mg
Glatiramer acetate	Reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis: Prefilled syringe: 20 mg SC once daily or 40 mg SC three times per week at least 48 hours apart	Safety and efficacy in children <18 years of age have not been established.	Injection: 20 mg/mL 40 mg/mL
Interferon β-1a	Treatment of patients with relapsing forms of multiple sclerosis: Injection (Rebif®): initial, 20% of maintenance dose; maintenance, 22 or 44 μg SC three times a week Injection (Avonex®): 30 μg IM once a week	Safety and efficacy in children <18 years of age have not been established.	Injection, IM (Avonex®): 30 μg/0.5mL 30 μg/vial Injection, SubQ (Rebif®): 22 μg/0.5 mL 44 μg/0.5 mL Titration pack: 8.8 μg/0.2 mL & 22 μg/0.5 mL
Interferon β-1b	Treatment of relapsing forms of multiple sclerosis: Vial: initial, 0.0625 mg SC every other day; maintenance, 0.25 mg SC every other day	Safety and efficacy in children <18 years of age have not been established.	Injection: 0.3 mg
Natalizumab	Treatment of relapsing forms of multiple sclerosis:	Safety and efficacy in children <18 years of	Injection: 300 mg/15 mL

Immunomodulatory Agents used to treat Multiple Sclerosis
AHFS Class 922000

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Vial: 300 mg intravenous infusion over one hour every four weeks	age have not been established.	
Peginterferon β -1a	Treatment of patients with relapsing forms of multiple sclerosis: Pen, prefilled syringe: initial, 63 μ g SC on day one, followed by 94 μ g SC on day 15, followed by 125 μ g SC on day 29 and then every 14 days thereafter	Safety and efficacy in children <18 years of age have not been established.	Injection: 125 μ g/0.5 mL Starter pack: 63 μ g/0.5 mL & 94 μ g/0.5 mL
Teriflunomide	Treatment of patients with relapsing forms of multiple sclerosis: Tablet: 7 mg or 14 mg QD	Safety and efficacy in children <18 years of age have not been established.	Tablet: 7 mg 14 mg

BID=twice daily, IM=intramuscular, SC=subcutaneous, QD=once daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the immunomodulatory agents used to treat multiple sclerosis are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Immunomodulatory Agents used to treat Multiple Sclerosis

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Relapsing-Remitting Multiple Sclerosis				
<p>Kappos et al.²⁸ (2015) DECIDE</p> <p>Daclizumab 150 mg SC every four weeks plus IM placebo once weekly</p> <p>vs</p> <p>IFNβ-1a 30 μg IM once weekly plus SC placebo every four weeks</p> <p>Patients were instructed to take prophylactic treatment for influenza-like symptoms during the first 24 weeks of therapy in order to reduce any potential for unbinding (interferon β-1a is associated with flu-like symptoms).</p>	<p>AC, DB, DD, MC, PG, RCT</p> <p>Patients 18 to 55 years of age with a diagnosis of RRMS, MRI showing lesions, EDSS score 0 to 5, two or more clinical relapses within the previous three years, with one clinical relapse occurring in the 12 months before randomization or one or more clinical relapses and at least one new lesion on MRI that was not associated with the clinical relapse within the previous two years with at least one of these events occurring in the 12 months before randomization</p>	<p>N=1,841</p> <p>96 to 144 weeks</p>	<p>Primary: Annualized relapse rate over a period of 144 weeks</p> <p>Secondary: Number of new or newly enlarged hyperintense lesions on T₂-weighted MRI scans of the brain (over a 96 week period), proportion of patients with confirmed progression of disability at 12 weeks (over a 144 week period), the proportion of patients who did not have a relapse (over a 144 week period), and the proportion of patients with an increase from baseline of at least 7.5 points on the MSIS-29 physical</p>	<p>Primary: The adjusted annualized relapse rate was 0.22 (95% CI, 0.19 to 0.24) in the daclizumab group and 0.39 (95% CI, 0.35 to 0.44) in the IFNβ-1a group. This represented a statistically significant, 45% reduction in the adjusted annualized relapse rate in favor of daclizumab compared to IFNβ-1a (P<0.001).</p> <p>Secondary: The number of new or newly enlarged hyperintense lesions on T₂-weighted images at week 96 was 4.3 (95% CI, 3.9 to 4.8) in the daclizumab group and 9.4 (95% CI, 8.5 to 10.5) in the IFNβ-1a group. This represented a statistically significant, 54% reduction in the number of new or newly enlarged in favor of daclizumab compared to IFNβ-1a (P<0.001).</p> <p>At week 144, the estimated percentage of patients who had disability progression confirmed at 12 weeks as measured by the EDSS was 16% in the daclizumab group and 20% in the IFNβ-1a group (HR, 0.84; 95% CI, 0.50 to 0.69; P=0.16).</p> <p>On the basis of the prespecified hierarchical testing plan, the results of the analyses of the third and fourth prespecified secondary end points were not considered to be significant.</p> <p>The estimated percentage of patients who were free from relapse at week 144 was 67% in the daclizumab group and 51% in the IFNβ-1a group (HR, 0.59; 95% CI, 0.50 to 0.69; P value no reported).</p> <p>Clinically meaningful worsening, defined as an increase of ≥7.5 points, in the patient-reported physical effect of multiple sclerosis, as assessed with the use of the MSIS-29 physical subscale, at week 96 was observed</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			subscale at 96 weeks, safety	in 19% of the patients in the daclizumab group and 23% of those in the IFNβ-1a group. This represented a 24% (95% CI, 5 to 40) reduction in the odds of worsening in favor of daclizumab compared to IFNβ-1a (P value not reported).
<p>Gold et al.²⁹ (2013) SELECT</p> <p>Daclizumab 150 mg SC every four weeks</p> <p>vs</p> <p>daclizumab 300 mg SC every four weeks</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 55 years of age with a diagnosis of RRMS, EDSS score 0 to 5, one clinical relapse occurring in the 12 months before randomization or at least one new gadolinium-enhancing lesion on the brain MRI within the six weeks before randomization</p>	<p>N=621</p> <p>52 weeks</p>	<p>Primary: Annualized relapsed rate at week 52</p> <p>Secondary: Cumulative number of new gadolinium-enhancing lesions on brain MRI scans done at weeks 8, 12, 16, 20 and 24, the number of new or newly enlarging T2 hyperintense lesions at week 52, the proportion of relapsing patients between baseline and week 52 and change in quality of life based on MSIS-29 score</p>	<p>Primary: The annualized relapse rate at 52 weeks was lower for patients in the daclizumab 150 mg group (0.21; 54% reduction), and in the daclizumab 300 mg group (0.23; 50 % reduction), compared to the placebo group (0.46; P<0.001 for both groups compared to placebo).</p> <p>Secondary: Cumulative number of new gadolinium-enhancing lesions on brain MRI scans done at weeks 8, 12, 16, 20 and 24, was lower in the daclizumab treatment groups compared to the placebo group (P<0.001).</p> <p>There was also a lower number of new or newly enlarging T2 hyperintense lesions, percentage change from baseline T2 hyperintense lesions percentage and change from baseline T1 hypointense lesions at week 52 at week 52 in the daclizumab treatment groups compared to the placebo group (P<0.001).</p> <p>From baseline to week 52, the estimated proportion of relapsing patients was reduced in the daclizumab treatment groups versus the placebo treatment groups (P=0.021 and P=0.091 in daclizumab 150 mg and daclizumab 300 mg groups, respectively).</p> <p>There was statistically significant improvement in the mean MSIS-29 physical score at week 52 for patients in the daclizumab 150 mg group versus those on placebo, but not for patients in the daclizumab 300 mg group (P=0.00082 and P=0.13 in daclizumab 150 mg and daclizumab 300 mg groups, respectively). There were similar improvements in other measure of quality of life, including measures of physical, psychological and overall health function.</p>
<p>Giovannoni et al.³⁰ (2014) SELECTION</p>	<p>DB, ES of SELECT³⁴ MC, RCT</p>	<p>N=517</p> <p>52 weeks</p>	<p>Primary: Safety and immunogenicity of treatment with</p>	<p>Primary: Frequency of adverse events was similar between the treatment initiation and continuous treatment groups.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Daclizumab 150 mg or 300 mg SC every four weeks with washout period of 20 weeks (new start or re-initiation group)</p> <p>vs</p> <p>daclizumab 150 mg or 300 mg SC every four weeks without washout period of 20 weeks (continuous treatment)</p>	<p>Patients who completed study treatment in the SELECT trial without a change in their overall health status that would preclude treatment with daclizumab</p>		<p>daclizumab</p> <p>Secondary: Durability of daclizumab treatment effect on disease activity, based on relapse activity (AAR and proportion of patients who relapsed), confirmed disability progression and MRI endpoints (new gadolinium enhancing lesions, new or enlarging T2 hyperintense lesions, total volume of T2 hyperintense lesions, volume of new T1 hypointense lesions, total volume of T1 hypointense lesions and whole brain volume)</p>	<p>Secondary: In continuous treatment group, ARR was similar between year one and year two. The numbers of new gadolinium enhancing lesions in this group were also consistent. The number of new or newly enhancing T2 hyperintense lesions that formed during year two was lower than year one, as was the volume of new T1 hypointense lesions. The proportion of patients who had confirmed disability progression was similar between year one and year two.</p> <p>In treatment initiation group, ARR, proportion on patients who relapsed and proportion of patients with confirmed disability progression were significantly reduced in year two. The number of new gadolinium-enhancing lesions and new or newly enlarging T2 lesions were also reduced in year two. Reductions were also recorded for the percentage change in volume of total T2 leases and the volume of new T1 hypointense lesions.</p>
<p>Gold et al.³¹ (2016) SELECTED</p> <p>Daclizumab 150 mg SC every four weeks</p>	<p>OL extension of SELECT and SELECTION trials</p> <p>Patients must have completed 52 weeks of both</p>	<p>N=410</p> <p>Up to 6.5 years</p>	<p>Primary: Safety</p> <p>Secondary: Efficacy</p>	<p>Primary: The yearly incidence of adverse events, serious adverse events, and adverse events leading to discontinuation did not increase over time and no deaths were reported. Forty-eight (12%) patients discontinued treatment due to adverse events. Common adverse events that occurred in 10% of patients or more were MS relapse (22%), nasopharyngitis (12%), and upper respiratory tract infection (12%). The most frequently reported</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>SELECT and SELECTION, been compliant with the SELECTION protocol, provided informed consent for SELECTED, and met other general eligibility criteria</p>			<p>serious adverse events excluding MS relapse, were hepatic enzyme elevations, pneumonia, ulcerative colitis, and urinary tract infection (each in three patients [each less than 1%]).</p> <p>Secondary: The adjusted ARR analyzed at 6-month intervals from the first dose of daclizumab was 0.21 (95% CI, 0.16 to 0.29) for weeks 0 to 24 and decreased to 0.15 (95% CI, 0.10 to 0.21) by the weeks 121 to 144 interval. The adjusted mean (95% CI) number of new/newly enlarging T2 hyperintense lesions was 1.95 (1.60 to 2.37) in year one and decreased to 1.26 (0.93 to 1.72) by year three of treatment with daclizumab. The mean annualized PBVC was -0.77% in year one and decreased to -0.32% by year three of treatment with daclizumab.</p>
<p>Giovannoni et al.³² (2014)</p> <p>Daclizumab 150 mg or 300 mg SC every four weeks in patients with highly active RRMS</p> <p>vs</p> <p>daclizumab 150 mg or 300 mg SC every four weeks in patients with less active RRMS</p>	<p>Post-hoc of SELECT³⁴</p> <p>Patients 18 to 55 years of age with a diagnosis of RRMS, EDSS score 0 to 5, one clinical relapse occurring in the 12 months before randomization or at least one new gadolinium-enhancing lesion on the brain MRI within the six weeks before randomization</p>	<p>N=621</p> <p>52 weeks</p>	<p>Primary: Annualized relapsed rate, new gadolinium-enhancing lesions, the number of new or newly enlarging T2 hyperintense lesions and disability progression</p> <p>Secondary: Not reported.</p>	<p>Primary: Treatment with daclizumab reduced ARR by 50% and 51% respectively in the highly active (P=0.0394) and less active (P<0.0001) treatment groups versus placebo, respectively.</p> <p>Treatment with daclizumab reduced new/newly-enlarging T2 lesions in highly active RRMS (76% reduction, P<0.0001) and less active RRMS (73% reduction, P<0.0001)</p> <p>Treatment with daclizumab reduced the risk of having more gadolinium-enhancing lesions in highly active RRMS (89% reduction, P<0.0001) and less active RRMS (86% reduction, P<0.0001)</p> <p>Treatment with daclizumab reduced the risk of sustained disability progression in highly active RRMS (88% reduction, P=0.0574) and less active RRMS (46% reduction, P=0.0383)</p> <p>Secondary: Not reported.</p>
<p>Gold et al.³³ (2012)</p> <p>DEFINE</p> <p>Dimethyl fumarate</p>	<p>DB, MC, PC, RCT</p> <p>Patients aged 18 to 55 years with a diagnosis of</p>	<p>N=1,237</p> <p>96 weeks</p>	<p>Primary: Proportion of patients who had a relapse by two years</p>	<p>Primary: Relapses after two years were observed in 27% and 26% of the patients in the twice daily and three times daily dimethyl fumarate groups, respectively, compared to 46% of patients in the placebo group (HR, 0.51; 95% CI: 0.39 to 0.65 and 0.50; 95% CI: 0.39 to 0.65, respectively).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>240 mg BID vs Dimethyl fumarate 240 mg TID vs placebo</p>	<p>RRMS, an EDSS score of 0 to 5, and at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization</p>		<p>Secondary: ARR, time to progression of disability, number of gadolinium-enhancing lesions and of new or enlarging hyperintense T2 lesions</p>	<p>Secondary: Time to first relapse was prolonged by 87 and 91 weeks in patients in the twice and three times daily groups, respectively, compared to placebo. Relative to placebo, the ARR was reduced by 53% and 48% in the twice daily and three times daily groups, respectively (P=0.001). Additionally, the time to progression of disability was reduced by 38% in the twice daily group (HR, 0.62; 95% CI: 0.44 to 0.87) and by 34% in the three times daily group (HR, 0.66; 95% CI: 0.48 to 0.92). Relative to placebo, the number of new or enlarging hyperintense T2 lesions and the number of gadolinium-enhancing lesions was decreased by 85% and 90%, respectively in patients receiving dimethyl fumarate twice daily and by 74% and 73% in patients receiving dimethyl fumarate three times daily (P<0.001 for all) The most common adverse events in patients receiving dimethyl fumarate were flushing, gastrointestinal events, proteinuria and pruritus.</p>
<p>Kappos et al.³⁴ (2010) FREEDOMS Fingolimod 0.5 mg once daily vs fingolimod 1.25 mg once daily vs placebo</p>	<p>DB, MC, PC, RCT Patients 18 to 55 years of age with RRMS and an EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past 2 years</p>	<p>N=1,272 24 months</p>	<p>Primary: ARR Secondary: Time to first relapse, proportion of patients relapse free after 24 months, time to confirmed disability (an increase ≥1 in EDSS) progression confirmed after three and six months, changes in EDSS and MSFC score from baseline to 24 months,</p>	<p>Primary: The aggregate ARR was lower with fingolimod 0.5 (0.18; 95% CI, 0.15 to 0.22) and 1.25 mg (0.16; 95% CI, 0.13 to 0.19) compared to placebo (0.40; 95% CI, 0.34 to 0.47; P<0.001 for both comparisons). This represents a reduction of 54 and 60%, respectively, in the ARR for fingolimod. A subgroup analysis comparing ARRs among treatment naïve patients and those previously treated found significant reductions compared to placebo (P<0.01 for all comparisons). Secondary: In the fingolimod groups compared to the placebo group, the time to a first relapse was longer (P<0.001 for both comparisons), the risk of relapse was reduced (0.5 mg vs placebo: HR, 0.48; 95% CI, 0.39 to 0.61; P<0.001 and 1.25 mg vs placebo: HR, 0.38; 95% CI, 0.30 to 0.48; P<0.001) and significantly more patients remained free of relapse during the 24 month period (0.5 mg: 70.4±2.3%; 95% CI, 66.0 to 74.8; P<0.001,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>number of gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing lesions, number of new or enlarged lesions on T2-weighted MRI scans, proportion of patients free from new or enlarged lesions on T2-weighted scans, volumes of hyperintense lesions on T2-weighted scans and hypointense lesions on T1-weighted scans, change in brain volume between baseline and 24 months, safety and tolerability</p>	<p>1.25 mg: 74.7±2.2%; 95% CI, 70.4 to 79.0; P<0.001, placebo: 45.6±2.3%; 95% CI, 40.7 to 50.6).</p> <p>The time to disability progression was longer in patients treated with fingolimod compared to patients treated with placebo. Treatment with fingolimod reduced the risk of disability progression, confirmed after three months, over the 24 month study period (HR, 0.70 for 0.5 mg and HR, 0.68 for 1.25 mg; P values not reported). The cumulative probability of disability progression (confirmed after three months) was 17.7% for fingolimod 0.5 mg, 16.6% for fingolimod 1.25 mg and 24.1% for placebo (P values not reported). Regarding disability progression that was confirmed after six months, the risk was also reduced with fingolimod over the 24 month study period (HR, 0.63 for 0.5 mg and HR, 0.60 for 1.25 mg; P values not reported), and the cumulative probability of progression was 12.5% for fingolimod 0.5 mg, 11.5% for fingolimod 1.25 mg and 19.0% for placebo (P values not reported).</p> <p>During the study period, the EDSS and MSFC scores remained stable or improved slightly in the fingolimod groups and worsened in the placebo group (P<0.02 for all comparisons).</p> <p>All MRI based secondary endpoints including number and proportion of patients demonstrating gadolinium-enhancing lesions, changes in hypointense and hyperintense lesions on T1- or T2-weighted scans and changes in brain volume favored the fingolimod groups compared to the placebo group (P≤0.03 for all comparisons).</p> <p>The rates of adverse events were reported to be similar (93 to 94%) among the three treatment groups. Adverse events that led to treatment discontinuation were more common with fingolimod 1.25 mg (14.2%) compared to fingolimod 0.5 mg (7.5%) and placebo (7.7%).</p> <p>The most common serious adverse events, each reported for eight patients, were bradycardia, MS relapse and basal-cell carcinoma. The overall incidence of infection was similar in the fingolimod and placebo groups (69 to 72%); serious infections occurred in 1.6 and 2.6% of patients.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results																																
				<p>Transient, dose-related decreases in heart rate occurred after the first dose of fingolimod was administered. Bradycardia was reported in nine patients receiving 0.5 mg of fingolimod, 14 patients receiving 1.25 mg of fingolimod and three patients receiving placebo.</p> <p>Macular edema was diagnosed in seven patients, all of whom were receiving 1.25 mg of fingolimod. Three of these events were reported as serious adverse events.</p> <p>Peripheral-blood lymphocyte counts were reduced from the baseline counts by an average of 73% with 0.5 mg of fingolimod and 76% with 1.25 mg of fingolimod, remaining stable after one month. Increases in ALT to three times the upper limit of normal or more were more frequent in the fingolimod groups (8.5% of patients in the 0.5 mg group and 12.5% of patients in the 1.25 mg group) than in the placebo group (1.7% of patients) and occurred predominantly in men.</p>																																
<p>Devonshire et al.³⁵ (2012) Subgroup analysis of FREEDOMS Fingolimod 0.5 mg once daily vs placebo Subgroup analysis based on demographic factors (sex, gender, treatment history), disease characteristics (baseline disability</p>	<p>DB, MC, PC, RCT Patients 18 to 55 years of age with RRMS and an EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past 2 years</p>	<p>N=1,272 24 months</p>	<p>Primary: ARR Secondary: Confirmed disability progression</p>	<p>Primary: Fingolimod 0.5 mg treatment significantly reduced ARR compared to placebo in all subgroups except for patients older than 40 years of age.</p> <p>ARR</p> <table border="1" data-bbox="1136 959 1780 1421"> <thead> <tr> <th>Subgroup</th> <th>HR, (95% CI)</th> </tr> </thead> <tbody> <tr> <td colspan="2">Sex</td> </tr> <tr> <td>Men</td> <td>0.33, (0.22 to 0.50)</td> </tr> <tr> <td>Women</td> <td>0.50, (0.39 to 0.65)</td> </tr> <tr> <td colspan="2">Age</td> </tr> <tr> <td>>40 years</td> <td>0.76, (0.54 to 1.09)</td> </tr> <tr> <td>≤40 years</td> <td>0.33, (0.25 to 0.43)</td> </tr> <tr> <td colspan="2">Treatment history</td> </tr> <tr> <td>Previously treated</td> <td>0.54, (0.39 to 0.74)</td> </tr> <tr> <td>Treatment naïve</td> <td>0.36, (0.27 to 0.49)</td> </tr> <tr> <td colspan="2">Number of relapses in year before study</td> </tr> <tr> <td>>1</td> <td>0.37, (0.27 to 0.51)</td> </tr> <tr> <td>≤1</td> <td>0.52, (0.39 to 0.69)</td> </tr> <tr> <td colspan="2">Number of relapses in two years before study</td> </tr> <tr> <td>>2</td> <td>0.50, (0.34 to 0.72)</td> </tr> <tr> <td>2</td> <td>0.45, (0.32 to 0.63)</td> </tr> </tbody> </table>	Subgroup	HR, (95% CI)	Sex		Men	0.33, (0.22 to 0.50)	Women	0.50, (0.39 to 0.65)	Age		>40 years	0.76, (0.54 to 1.09)	≤40 years	0.33, (0.25 to 0.43)	Treatment history		Previously treated	0.54, (0.39 to 0.74)	Treatment naïve	0.36, (0.27 to 0.49)	Number of relapses in year before study		>1	0.37, (0.27 to 0.51)	≤1	0.52, (0.39 to 0.69)	Number of relapses in two years before study		>2	0.50, (0.34 to 0.72)	2	0.45, (0.32 to 0.63)
Subgroup	HR, (95% CI)																																			
Sex																																				
Men	0.33, (0.22 to 0.50)																																			
Women	0.50, (0.39 to 0.65)																																			
Age																																				
>40 years	0.76, (0.54 to 1.09)																																			
≤40 years	0.33, (0.25 to 0.43)																																			
Treatment history																																				
Previously treated	0.54, (0.39 to 0.74)																																			
Treatment naïve	0.36, (0.27 to 0.49)																																			
Number of relapses in year before study																																				
>1	0.37, (0.27 to 0.51)																																			
≤1	0.52, (0.39 to 0.69)																																			
Number of relapses in two years before study																																				
>2	0.50, (0.34 to 0.72)																																			
2	0.45, (0.32 to 0.63)																																			

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results																																								
scores, relapse rates, and lesion parameters), and response to previous therapy.				<table border="1"> <tr> <td>I</td> <td>0.37, (0.24 to 0.58)</td> </tr> <tr> <td colspan="2">Baseline disability</td> </tr> <tr> <td>EDSS >3.5</td> <td>0.34, (0.20 to 0.58)</td> </tr> <tr> <td>EDSS 0 to 3.5</td> <td>0.48, (0.38 to 0.60)</td> </tr> <tr> <td colspan="2">Number of gadolinium-enhancing lesions</td> </tr> <tr> <td>≥1</td> <td>0.40, (0.29 to 0.55)</td> </tr> <tr> <td>0</td> <td>0.48, (0.36 to 0.65)</td> </tr> <tr> <td colspan="2">T2 lesion volume</td> </tr> <tr> <td>>3,300 mm</td> <td>0.47, (0.36 to 0.63)</td> </tr> <tr> <td>≤3,300 mm</td> <td>0.40, (0.29 to 0.57)</td> </tr> <tr> <td colspan="2">Disease activity in treatment-naïve or previously treated patients</td> </tr> <tr> <td>Group A*</td> <td>0.29, (0.16 to 0.52)</td> </tr> <tr> <td>Group B†</td> <td>0.38, (0.24 to 0.62)</td> </tr> <tr> <td>Group C‡</td> <td>0.38, (0.21 to 0.68)</td> </tr> <tr> <td>Group D§</td> <td>0.49, (0.31 to 0.78)</td> </tr> <tr> <td>Group E </td> <td>0.33, (0.18 to 0.62)</td> </tr> </table>	I	0.37, (0.24 to 0.58)	Baseline disability		EDSS >3.5	0.34, (0.20 to 0.58)	EDSS 0 to 3.5	0.48, (0.38 to 0.60)	Number of gadolinium-enhancing lesions		≥1	0.40, (0.29 to 0.55)	0	0.48, (0.36 to 0.65)	T2 lesion volume		>3,300 mm	0.47, (0.36 to 0.63)	≤3,300 mm	0.40, (0.29 to 0.57)	Disease activity in treatment-naïve or previously treated patients		Group A*	0.29, (0.16 to 0.52)	Group B†	0.38, (0.24 to 0.62)	Group C‡	0.38, (0.21 to 0.68)	Group D§	0.49, (0.31 to 0.78)	Group E	0.33, (0.18 to 0.62)								
				I	0.37, (0.24 to 0.58)																																							
				Baseline disability																																								
				EDSS >3.5	0.34, (0.20 to 0.58)																																							
				EDSS 0 to 3.5	0.48, (0.38 to 0.60)																																							
				Number of gadolinium-enhancing lesions																																								
				≥1	0.40, (0.29 to 0.55)																																							
				0	0.48, (0.36 to 0.65)																																							
				T2 lesion volume																																								
				>3,300 mm	0.47, (0.36 to 0.63)																																							
				≤3,300 mm	0.40, (0.29 to 0.57)																																							
				Disease activity in treatment-naïve or previously treated patients																																								
				Group A*	0.29, (0.16 to 0.52)																																							
				Group B†	0.38, (0.24 to 0.62)																																							
				Group C‡	0.38, (0.21 to 0.68)																																							
				Group D§	0.49, (0.31 to 0.78)																																							
				Group E	0.33, (0.18 to 0.62)																																							
				<p>Secondary: Disability progression confirmed after three months</p> <table border="1"> <thead> <tr> <th>Subgroup</th> <th>HR, (95% CI)</th> </tr> </thead> <tbody> <tr> <td colspan="2">Sex</td> </tr> <tr> <td>Men</td> <td>0.43, (0.22 to 0.81)</td> </tr> <tr> <td>Women</td> <td>0.77, (0.53 to 1.10)</td> </tr> <tr> <td colspan="2">Age</td> </tr> <tr> <td>>40 years</td> <td>0.74, (0.46 to 1.19)</td> </tr> <tr> <td>≤40 years</td> <td>0.68, (0.45 to 1.02)</td> </tr> <tr> <td colspan="2">Treatment history</td> </tr> <tr> <td>Previously treated</td> <td>0.70, (0.43 to 1.14)</td> </tr> <tr> <td>Treatment naïve</td> <td>0.63, (0.41 to 0.95)</td> </tr> <tr> <td colspan="2">Number of relapses in year before study</td> </tr> <tr> <td>>1</td> <td>0.62, (0.37 to 1.05)</td> </tr> <tr> <td>≤1</td> <td>0.70, (0.47 to 1.03)</td> </tr> <tr> <td colspan="2">Number of relapses in two years before study</td> </tr> <tr> <td>>2</td> <td>0.40, (0.21 to 0.77)</td> </tr> <tr> <td>2</td> <td>0.71, (0.44 to 1.13)</td> </tr> <tr> <td>1</td> <td>0.84, (0.46 to 1.52)</td> </tr> <tr> <td colspan="2">Baseline disability</td> </tr> <tr> <td>EDSS >3.5</td> <td>0.32, (0.14 to 0.73)</td> </tr> <tr> <td>EDSS 0 to 3.5</td> <td>0.77, (0.55 to 1.09)</td> </tr> </tbody> </table>	Subgroup	HR, (95% CI)	Sex		Men	0.43, (0.22 to 0.81)	Women	0.77, (0.53 to 1.10)	Age		>40 years	0.74, (0.46 to 1.19)	≤40 years	0.68, (0.45 to 1.02)	Treatment history		Previously treated	0.70, (0.43 to 1.14)	Treatment naïve	0.63, (0.41 to 0.95)	Number of relapses in year before study		>1	0.62, (0.37 to 1.05)	≤1	0.70, (0.47 to 1.03)	Number of relapses in two years before study		>2	0.40, (0.21 to 0.77)	2	0.71, (0.44 to 1.13)	1	0.84, (0.46 to 1.52)	Baseline disability		EDSS >3.5	0.32, (0.14 to 0.73)	EDSS 0 to 3.5	0.77, (0.55 to 1.09)
					Subgroup	HR, (95% CI)																																						
					Sex																																							
					Men	0.43, (0.22 to 0.81)																																						
					Women	0.77, (0.53 to 1.10)																																						
					Age																																							
					>40 years	0.74, (0.46 to 1.19)																																						
					≤40 years	0.68, (0.45 to 1.02)																																						
					Treatment history																																							
					Previously treated	0.70, (0.43 to 1.14)																																						
					Treatment naïve	0.63, (0.41 to 0.95)																																						
					Number of relapses in year before study																																							
					>1	0.62, (0.37 to 1.05)																																						
					≤1	0.70, (0.47 to 1.03)																																						
					Number of relapses in two years before study																																							
>2	0.40, (0.21 to 0.77)																																											
2	0.71, (0.44 to 1.13)																																											
1	0.84, (0.46 to 1.52)																																											
Baseline disability																																												
EDSS >3.5	0.32, (0.14 to 0.73)																																											
EDSS 0 to 3.5	0.77, (0.55 to 1.09)																																											

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results																								
				<table border="1"> <thead> <tr> <th colspan="2">Number of gadolinium-enhancing lesions</th> </tr> </thead> <tbody> <tr> <td>≥1</td> <td>0.62, (0.37 to 1.04)</td> </tr> <tr> <td>0</td> <td>0.75, (0.50 to 1.11)</td> </tr> <tr> <th colspan="2">T2 lesion volume</th> </tr> <tr> <td>>3,300 mm</td> <td>0.59, (0.38 to 0.90)</td> </tr> <tr> <td>≤3,300 mm</td> <td>0.85, (0.53 to 1.36)</td> </tr> <tr> <th colspan="2">Disease activity in treatment-naïve or previously treated patients</th> </tr> <tr> <td>Group A*</td> <td>0.64, (0.27 to 1.51)</td> </tr> <tr> <td>Group B†</td> <td>0.59, (0.29 to 1.20)</td> </tr> <tr> <td>Group C‡</td> <td>0.68, (0.29 to 1.62)</td> </tr> <tr> <td>Group D§</td> <td>0.54, (0.26 to 1.10)</td> </tr> <tr> <td>Group E </td> <td>0.73, (0.25 to 2.07)</td> </tr> </tbody> </table> <p>*Patients who received interferon beta during the year before study enrollment but who had as many or more relapses in the year immediately before the study than in the two years before the study. †Patients who received any disease modifying therapy during the year before study enrollment but who had as many or more relapses in the year immediately before the study than in the two years before the study. ‡ Patients who received interferon beta during the year before study enrollment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline. § Patients who received any disease modifying therapy during the year before study enrollment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline. Treatment-naïve rapidly evolving severe RRMS with at least two relapses within the year before baseline and at least one gadolinium-enhancing lesion at baseline.</p>	Number of gadolinium-enhancing lesions		≥1	0.62, (0.37 to 1.04)	0	0.75, (0.50 to 1.11)	T2 lesion volume		>3,300 mm	0.59, (0.38 to 0.90)	≤3,300 mm	0.85, (0.53 to 1.36)	Disease activity in treatment-naïve or previously treated patients		Group A*	0.64, (0.27 to 1.51)	Group B†	0.59, (0.29 to 1.20)	Group C‡	0.68, (0.29 to 1.62)	Group D§	0.54, (0.26 to 1.10)	Group E	0.73, (0.25 to 2.07)
Number of gadolinium-enhancing lesions																												
≥1	0.62, (0.37 to 1.04)																											
0	0.75, (0.50 to 1.11)																											
T2 lesion volume																												
>3,300 mm	0.59, (0.38 to 0.90)																											
≤3,300 mm	0.85, (0.53 to 1.36)																											
Disease activity in treatment-naïve or previously treated patients																												
Group A*	0.64, (0.27 to 1.51)																											
Group B†	0.59, (0.29 to 1.20)																											
Group C‡	0.68, (0.29 to 1.62)																											
Group D§	0.54, (0.26 to 1.10)																											
Group E	0.73, (0.25 to 2.07)																											
<p>Kappos et al.³⁶ (2006)</p> <p>Fingolimod 1.25 mg once daily</p> <p>vs</p> <p>fingolimod 5 mg once daily</p>	<p>DB, ES, MC, PC, RCT</p> <p>Patients 18 to 60 years of age with RRMS, an EDSS score 0 to 6, neurologically stable condition with no evidence</p>	<p>N=281</p> <p>6 months (followed by a 6 month ES)</p>	<p>Primary:</p> <p>Total number of gadolinium-enhanced lesions/patient recorded on T1-weighted MRI intervals for six months</p> <p>Secondary:</p>	<p>Primary:</p> <p>The total cumulative numbers of lesions per patient on post-baseline, monthly gadolinium-enhanced T1-weighted MRI scans were lower in both fingolimod groups compared to the placebo group (P<0.001 for 1.25 mg and P=0.006 for 5 mg).</p> <p>Secondary:</p> <p>At 12 months, the number of lesions remained low in the two groups of patients who received continuous treatment with fingolimod, whereas the number decreased significantly in the placebo-to-fingolimod group (P</p>																								

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs placebo</p> <p>Patients who were randomized to placebo for the first six months were randomized to active treatment during the six month ES (placebo/fingolimod group).</p>	<p>of relapse for ≥ 30 days before screening and ≥ 2 documented relapses during the previous two years; ≥ 1 documented relapse in the year before enrollment or ≥ 1 gadolinium-enhanced lesions detected by MRI at screening</p>		<p>Total number of gadolinium-enhanced lesions per patient, the proportion of patients with gadolinium-enhanced lesions, total number of new lesions per patient on T2-weighted images, changes in lesion volume on T2-weighted images, brain volume from baseline to month six, number of patients remaining free of relapse, ARR, time to first relapse, disability scores</p>	<p>value not reported).</p> <p>At six months, the proportion of patients who were free of gadolinium-enhanced lesions was greater in both fingolimod groups than with the placebo group ($P < 0.001$ for both comparisons), with a separation between the curves becoming evident after two months of treatment.</p> <p>With the exception of the change in brain volume from baseline, all secondary MRI endpoints differed significantly between the fingolimod groups and the placebo group, in each case favoring treatment with fingolimod.</p> <p>At 12 months, MRI variables consistently demonstrated that fingolimod continued to have a marked effect on inflammatory activity, as reflected by MRI findings. At 12 months, more than 80% of patients who received fingolimod were free of gadolinium-enhanced lesions.</p> <p>The trial was not powered to detect a treatment effect on relapse endpoints; however, in both groups of patients who received continuous fingolimod, 79% were free of relapse at month 12, whereas 65 to 67% were free of relapse in the placebo-to-fingolimod group.</p> <p>Significant improvements over placebo were observed in the fingolimod groups, including a reduction in the ARR (by 53% in the 5 mg group and by 55% in the 1.25 mg group). For the placebo-to-fingolimod group, the ARR was lower during the period of treatment with fingolimod. The relapse rates for patients who received continuous fingolimod remained low during months seven to 12, with overall 12 month relapse rates of 0.31 and 0.29 for the 1.25 and 5 mg dose, respectively.</p> <p>The estimated time to a first relapse was significantly prolonged in the fingolimod groups (P value not reported).</p> <p>There were no significant differences in EDSS scores at 12 months between the fingolimod groups and the placebo/fingolimod group ($P = 0.74$ for 1.25 mg and $P = 0.64$ for 5 mg).</p>
Radue et al. ³⁷	DB, MC, PC, RCT	N=1,272	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2012)</p> <p>Fingolimod 0.5 mg QD</p> <p>vs</p> <p>Fingolimod 1.25 mg QD</p> <p>vs</p> <p>placebo</p>	<p>Patients 18 to 55 years of age with RRMS and an EDSS score 0 to 5.5 and ≥ 1 relapse in the past year or ≥ 2 relapses in the past 2 years</p>	<p>2 years</p>	<p>Proportion of patients free from gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing T1 lesions or new anti-inflammatory activity, proportion of patients free from new or enlarged T2 lesions, change from baseline in the total volume of T2 lesions or T1 hypointense lesions, change in PBVC</p> <p>Secondary: Not reported</p>	<p>Both fingolimod 0.5 mg and 1.25 mg significantly decreased the number of new/newly enlarged T2 lesions, the number of gadolinium-enhancing lesions and the volume of gadolinium-enhancing lesions from baseline over 24 months compared to placebo ($P < 0.001$ for all). Additionally, the proportion of patients free from new/newly enlarged T2 lesions, gadolinium-enhancing lesions or both was significantly greater in patients receiving fingolimod compared to placebo ($P < 0.001$ for all)</p> <p>Change in T2 lesion volume was significantly reduced in each fingolimod group compared to placebo at both 12 and 24 months ($P < 0.001$ for all). The actual T2 lesions volume slightly decreased in each fingolimod group, but increased in the placebo group.</p> <p>After 24 months, T1 hypointense lesion volume increased in the placebo group, but remained stable in each fingolimod group (absolute change vs placebo, $P < 0.001$ for each).</p> <p>Both fingolimod groups significantly reduced PBVC compared to placebo from months 0 to 6, 0 to 12 and 12 to 24 ($P < 0.05$ for all).</p> <p>Secondary: Not reported</p>
<p>Saida et al.³⁸ (2012)</p> <p>Fingolimod 0.5 mg QD</p> <p>vs</p> <p>Fingolimod 1.25 mg QD</p> <p>vs</p>	<p>PC, PG, RCT</p> <p>Patients aged 18 to 60 years, a diagnosis of MS according to the revised McDonald criteria and a relapsing course of the disease</p>	<p>N=171</p> <p>6 months</p>	<p>Primary: Percentage of patients free from gadolinium-enhanced lesions at months three and six</p> <p>Secondary: Relapses over six months, safety</p>	<p>Primary: The proportion of patients who were free from gadolinium-enhanced lesions at months three and six was significantly greater in the fingolimod 0.5 mg (70%) and 1.25 mg (86%) groups compared to placebo (40%; $P < 0.004$ and $P < 0.001$, respectively).</p> <p>Secondary: The proportion of patients who were relapse free in the fingolimod 0.5 mg and 1.25 mg groups was 78.9% and 83.3%, respectively, compared to 64.9% in the placebo group (OR, 1.94; 95% CI: 0.82 to 4.63 and OR, 2.49; 95% CI: 0.99 to 6.29, respectively).</p> <p>An adverse event was reported in 91.2% and 94.4% of patients receiving</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo</p>				<p>fingolimod 0.5 mg and 1.25 mg, respectively, compared to 78.9% of patients receiving placebo (No P values reported). Additionally, a serious adverse event was reported in 8.8% and 20.4% of patients receiving fingolimod 0.5 mg and 1.25 mg, respectively, compared to 5.3% of patients receiving placebo (No P values reported). Adverse events related to fingolimod included transient bradycardia and atrioventricular block at treatment initiation and elevated liver enzymes.</p>
<p>Cohen et al.³⁹ (2010) TRANSFORMS</p> <p>Fingolimod 0.5 mg once daily</p> <p>vs</p> <p>fingolimod 1.25 mg once daily</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 µg IM once-weekly</p> <p>Previous or recent therapy with any type of IFNβ or GA was not a criterion for exclusion.</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past two years</p>	<p>N=1,292</p> <p>12 months</p>	<p>Primary: ARR</p> <p>Secondary: The number of new or enlarged hyperintense lesions on T2-weighted MRI scans at 12 months, time to confirmed disability progression and adverse events</p>	<p>Primary: There were significantly greater reductions in ARR for both fingolimod groups compared to the IFNβ-1a group (fingolimod 1.25 mg: ARR, 0.20; 95% CI, 0.16 to 0.26; P<0.001, fingolimod 0.5 mg: ARR, 0.16; 95% CI, 0.12 to 0.21; P<0.001, IFNβ-1a: ARR, 0.33; 95% CI, 0.26 to 0.42).</p> <p>There was no significant difference in the magnitude of the treatment effect between patients who had previously undergone disease treatment and those who had not.</p> <p>Secondary: Patients in the two fingolimod groups had significantly fewer new or enlarged hyperintense lesions on T2-weighted images at 12 months compared to those in the IFN group (fingolimod 1.25 mg: 1.5±2.7; P<0.001, fingolimod 0.5 mg: 1.7±3.9; P=0.004 and IFNβ-1a: 2.6±5.8).</p> <p>Confirmed disability progression was infrequent in all the treatment groups. There were no significant differences in the time to the progression of disability or in the proportion of patients with confirmed progression among the treatment groups (P values not reported).</p> <p>Adverse events were reported in similar proportions of patients in the three treatment groups, ranging from 86 to 92%. Serious adverse events and those leading to the discontinuation of a study drug were most frequent in patients assigned to fingolimod 1.25 mg. The most common adverse events observed were bradycardia and atrioventricular block.</p> <p>The overall incidence of infection was similar across the treatment groups (ranging from 51 to 53%).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>Increases in mean arterial pressure occurred in both fingolimod groups (3 mm Hg in the 1.25 mg group and 2 mm Hg in the 0.5 mg group) during the first six months and remained stable between six and 12 months.</p> <p>Macular edema was confirmed in six patients receiving fingolimod; four patients in the 1.25 mg group (1%) and two patients in the 0.5 mg group (0.5%).</p> <p>A mild reduction (2 to 3%) in the mean forced respiratory volume in one second was observed in both fingolimod groups at one month, with no further reductions for the remainder of treatment.</p>
<p>Khatri et al.⁴⁰ (2011) TRANSFORMS</p> <p>Fingolimod 0.5 mg once daily</p> <p>vs</p> <p>fingolimod 1.25 mg once daily</p> <p>Patients initially randomized to either fingolimod dose in the core study continued treatment throughout the extension period.</p> <p>Patients initially randomized IFNβ-1a 30 μg IM once-weekly were randomly reassigned (1:1) to receive</p>	<p>DB, DD, ES, MC, PG, RCT</p> <p>A 12-month extension of TRANSFORMS; patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past two years; all patients must have completed the core study on assigned treatments</p>	<p>N=1,027</p> <p>24 months</p>	<p>Primary: ARR</p> <p>Secondary: The number of new or enlarged hyperintense lesions on T2-weighted MRI scans at 12 months, time to confirmed disability progression, adverse events</p>	<p>Primary: Patients initially randomized to fingolimod 0.5 or 1.25 mg in the core study continued to experience reductions in ARR throughout the extension study (months 13 to 24). The estimated ARR for patients receiving fingolimod 0.5 mg was not different between the core study and 12 month extension period (0.12 vs 0.11, respectively; P=0.80). Similarly, there was no difference in the ARR for patients continuing the 1.25 mg dose through month 24 compared to the core study (0.15 vs 0.11 for, respectively; P=0.12).</p> <p>Patients switched from IFNβ-1a to either fingolimod dose in the extension period experienced greater reductions in ARR compared to initial treatment with IFNβ-1a. Patients switched to fingolimod 0.5 mg experience a lower ARR in the extension period compared to treatment with IFNβ-1a during the core trial (0.22 vs 0.31; P=0.049). Patients switched from IFNβ-1a to fingolimod 1.25 mg had lower ARR in the extension period with fingolimod treatment compared to treatment with IFNβ-1a in the core trial (0.18 vs 0.29; P=0.024). Switching from IFNβ-1a to fingolimod 0.5 mg was associated with a 30% reduction in relapse rates (ARR, 0.70; 95% CI, 0.49 to 1.00), while patients switched to the 1.25 mg dose experienced a 36% reduction in relapses (ARR, 0.64; 95% CI, 0.43 to 0.94).</p> <p>Secondary: Patients in the fingolimod 1.25 mg continuous treatment group had significantly fewer (mean) new or enlarged hyperintense lesions on T2-</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p> fingolimid 0.5 or 1.25 mg daily for the duration of the extension period.</p>				<p>weighted images at 24 months compared to the end of the core study (1.0±2.3 vs 1.4±2.37; P=0.0003). Significant reductions in new or enlarged lesions were also observed in patients treated with the 0.5 mg dose at 24 months compared to month 12 (0.9±1.87 vs 1.6±3.60; P=0.0001).</p> <p>Patients switched from IFNβ-1a to either fingolimid dose for the extension period experienced significant reductions in new or enhanced T2 lesions at 24 months compared to initial treatment with IFNβ-1a in the core study (1.0 vs 2.4 and 0.7 vs 2.1 for the 1.25 and 0.5 mg doses, respectively; P<0.0001 for both comparisons). There were no significant changes in EDSS scores in the extension period compared to the core study for any of the treatments.</p> <p>Patients switched from IFNβ-1a to fingolimid experienced fewer adverse events compared to treatment with IFNβ-1a in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; P values not reported). Fewer patients continuing fingolimid from the core study reported adverse events in the extension period compared to the core study. (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; P values not reported).</p> <p>There was a rise in serious cardiac-related adverse events after switching to fingolimid 1.25 mg (from 0% with IFNβ-1a to 2% with fingolimid) but not with the 0.5 mg dose (1% for both time periods).</p>
<p>Cohen et al.⁴¹ (2016) TRANSFORMS</p> <p>Fingolimid 0.5 mg once daily</p> <p>vs</p> <p>fingolimid 1.25 mg once daily</p>	<p>DB, DD, ES, MC, PG, RCT</p> <p>A long-term extension of TRANSFORMS; patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2</p>	<p>N=772</p> <p>Up to 4.5 years</p>	<p>Primary: ARR</p> <p>Secondary: The number of new or enlarged hyperintense lesions on T2-weighted MRI scans at 12 months, time to confirmed disability</p>	<p>Primary: Patients in the continuous-fingolimid group who received treatment for up to 4.5 years demonstrated significantly lower ARR compared with those in the IFN-switch group (0.17 vs 0.27), with an associated 35% reduction in the risk of relapse (HR, 0.65; P<0.001). Within-group comparisons in the IFN-switch group showed a reduction in ARR from 0.40 to 0.20 after patients switched to fingolimid. In the continuous-fingolimid group, the low relapse rate during the extension phase (0.16) was comparable with that observed in the core phase (0.19).</p> <p>Secondary: New/newly enlarging T2 lesion counts remained low in the continuous-</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results																														
<p>Patients initially randomized to either fingolimod dose in the core study continued treatment throughout the extension period.</p> <p>Patients initially randomized IFNβ-1a 30 µg IM once-weekly were randomly reassigned (1:1) to receive fingolimod 0.5 or 1.25 mg daily for the duration of the extension period.</p>	<p>relapses in the past two years; all patients must have completed the core study on assigned treatments</p>		<p>progression, adverse events</p>	<p>fingolimod group throughout the extension phase. The percentage of patients free of new/newly enlarging T2 lesions between the groups was similar throughout the extension study (continuous-fingolimod group: 42%; IFN-switch group: 45%; P=0.63).</p> <p>HRs for confirmed disability progression were not statistically different at end of study in the continuous-fingolimod versus the IFN-switch group (HR 3-month confirmed disability progression, 0.94; CI, 0.71 to 1.26; P=0.687; 6-month confirmed disability progression, 1.08; CI, 0.77 to 1.51; P=0.674).</p> <p>The highest incidence of adverse events during the extension phase was reported for nasopharyngitis, lymphocyte count decrease and headache. The proportion of patients who discontinued the study because of adverse events was similar between the treatment groups (8.4% in the continuous-fingolimod group, 7.8% in the IFN-switch group), mostly due to an increase in liver enzymes by >5-fold of the upper limit of normal.</p>																														
<p>Meca-Lallana et al.⁴² (2012)</p> <p>GA</p> <p>Patients must have switched from treatment with IFNβ and been on GA for at least 24 weeks.</p>	<p>MC, OS</p> <p>Patients aged 18 to 60 years with a diagnosis of RRMS, a score of ≤5.5 on the Kurtzke EDSS and confirmed spasticity</p>	<p>N=68</p> <p>6 months</p>	<p>Primary: Changes on the PSFS, MAS, ATRS and GPS after three and six months</p> <p>Secondary: Change in disability, number of relapses, working days' leave, adverse events</p>	<p>Primary: Significant reductions from baseline in mean scores on all spasticity measurement scales were observed after three and six months.</p> <table border="1" data-bbox="1136 959 1917 1182"> <thead> <tr> <th>Scale</th> <th>Baseline</th> <th>Three Months</th> <th>P Value (Three Months)</th> <th>Six Months</th> <th>P Value (Six Months)</th> </tr> </thead> <tbody> <tr> <td>PSFS</td> <td>1.7</td> <td>1.4</td> <td><0.01</td> <td>1.3</td> <td><0.01</td> </tr> <tr> <td>MAS</td> <td>0.7</td> <td>0.6</td> <td><0.01</td> <td>0.5</td> <td><0.01</td> </tr> <tr> <td>ATRS</td> <td>1.6</td> <td>1.4</td> <td><0.01</td> <td>1.3</td> <td><0.01</td> </tr> <tr> <td>GPS</td> <td>29.4</td> <td>24.7</td> <td><0.01</td> <td>19.1</td> <td><0.01</td> </tr> </tbody> </table> <p>Secondary: EDSS scores were significantly decreased after three months but not after six months (P<0.05 and P=0.385, respectively). A relapse was observed in 10.3% of patients over six months.</p> <p>After three months, 19.1% of patients reported missing work and after SIX months, 13.2% more patients reported missing work. The mean</p>	Scale	Baseline	Three Months	P Value (Three Months)	Six Months	P Value (Six Months)	PSFS	1.7	1.4	<0.01	1.3	<0.01	MAS	0.7	0.6	<0.01	0.5	<0.01	ATRS	1.6	1.4	<0.01	1.3	<0.01	GPS	29.4	24.7	<0.01	19.1	<0.01
Scale	Baseline	Three Months	P Value (Three Months)	Six Months	P Value (Six Months)																													
PSFS	1.7	1.4	<0.01	1.3	<0.01																													
MAS	0.7	0.6	<0.01	0.5	<0.01																													
ATRS	1.6	1.4	<0.01	1.3	<0.01																													
GPS	29.4	24.7	<0.01	19.1	<0.01																													

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>number of working days' leave used was 15.4 and 26.5 days, at three and six months, respectively.</p> <p>At least one adverse event was reported in five (7.4%) of patients, however only one was considered possibly related to GA.</p>
<p>Ford et al.⁴³ (2010)</p> <p>GA 20 mg SC daily</p> <p>vs</p> <p>placebo</p>	<p>ES, OL, PRO</p> <p>Patients with RRMS who had experienced ≥ 2 medically documented relapses in the previous two years and had EDSS scores 0 to 5 at study entry</p>	<p>N=100</p> <p>180 months</p>	<p>Primary: Change from baseline in ARR, change in EDSS scores, yearly EDSS scores</p> <p>Secondary: Not reported</p>	<p>Primary: The cohort of patients continuing to receive GA for 15 year had a lower ARR compared to their baseline values (0.25 ± 0.34 vs 1.12 ± 0.82; P value not reported). These results appear to be lower compared to reductions in AAR for patients completing the original study but who did not remain on treatment for 15 years (0.43 ± 0.58 vs 1.18 ± 0.82; P value not reported), although the significance the lowered relapse rate in these patients is unknown. Of patients who withdrew from the original study, the ARR associated with GA treatment was 0.56 ± 0.68 compared to baseline relapse rates of 1.23 ± 0.83 (P value not reported).</p> <p>The cohort of patients continuing GA treatment for 15 years had a slower progression in EDSS scores compared to the modified ITT population of patients completing the original study, and the population of patients who withdrew from the original study (0.6 ± 2.0 vs 0.9 ± 1.8 and 1.0 ± 1.7 points, respectively; P value not reported).</p> <p>Moreover, the average yearly change in EDSS was smaller with the cohort of patients continuing GA treatment for 15 years compared to the original modified ITT population completing the original study, and the population of patients who withdrew from the original study (0.1 ± 0.2 vs 0.2 ± 0.6 and 0.5 ± 0.8, respectively; P value not reported)</p> <p>Secondary: Not reported</p>
<p>Boneschi et al.⁴⁴ (2003)</p> <p>GA 20 mg SC daily</p> <p>vs</p>	<p>MA</p> <p>DB, PC, RCTs of patients 18 to 50 years of age with RRMS for at least one year with ≥ 1</p>	<p>N=540 (3 studies)</p> <p>Up to 35 months</p>	<p>Primary: ARR</p> <p>Secondary: Total number of relapses, time to first relapse and</p>	<p>Primary: Treatment with GA was associated with a statistically significant 28% reduction in the ARR compared to treatment with placebo (0.82 vs 1.14; $P=0.004$).</p> <p>Secondary: Treatment with GA was associated with a statistically significant 36%</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	relapse in the previous two years		disability progression	<p>reduction in the total number of relapses compared to treatment with placebo (P<0.0001).</p> <p>Treatment with GA was associated with a statistically significant 32% delay in the time to first relapse compared to treatment with placebo (322 vs 219 days; P=0.01).</p> <p>Treatment with GA was associated with a beneficial effect on disability progression compared to treatment with placebo (RR, 0.6; 95% CI, 0.4 to 0.9; P=0.02).</p>
<p>Caon et al.⁴⁵ (2006)</p> <p>GA 20 mg SC daily</p> <p>Administered for up to 42 months to patients who had previously received IFNβ-1a 30 μg IM once-weekly therapy for up to 24 months.</p>	<p>OL, PRO</p> <p>Patients 18 years of age or older with RRMS</p>	<p>N=85</p> <p>Up to 24 months</p>	<p>Primary: ARR</p> <p>Secondary: Change in EDSS</p>	<p>Primary: Switching to GA was associated with a statistically significant 57% reduction in the ARR from 1.23 to 0.53 (P=0.0001).</p> <p>In a subgroup of patients who switched to GA due to lack of efficacy with IFNβ-1a, the ARR was reduced from 1.32 to 0.52 (61%; P=0.0001).</p> <p>There was no statistically significant reduction in the ARR among patients who switched from IFNβ-1a to GA due to adverse effects (P=NS).</p> <p>Secondary: After 37.5 months of GA there was a statistically significant improvement in mean EDSS scores (P=0.0001).</p>
<p>Zwibel et al.⁴⁶ (2006)</p> <p>GA 20 mg SC daily administered to treatment naïve patients</p> <p>vs</p> <p>GA 20 mg SC daily administered to patients who had</p>	<p>MC, OL, PRO</p> <p>Patients 18 years of age or older with RRMS and an EDSS disability score ≤6</p>	<p>N=805</p> <p>3.5 years</p>	<p>Primary: ARR, proportion of relapse-free patients, time to first relapse, progression of neurological disability (measured by change in EDSS score from baseline) and proportion of</p>	<p>Primary: There was no significant difference between the prior IFNβ-1b and treatment-naïve groups in the reduction of ARR from two years before study entry (75% in both groups; P=0.148).</p> <p>No significant difference was reported between the prior IFNβ-1b and treatment-naïve groups in the proportion of relapse-free patients throughout the study (68.4 vs 69.5%; P>0.90).</p> <p>There were no differences in the estimated time to first relapse for 25% of patients in the prior IFNβ-1b and treatment-naïve groups (245 vs 328 days, respectively; P=0.28).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
previously received IFNβ-1b therapy			patients with sustained progression (≥ 1 EDSS point increase for six months) Secondary: Not reported	Patients with a prior history of IFNβ-1b therapy exhibited a higher rate of neurological disability progression at 12 and 18-months and last observation compared to treatment-naïve patients (P=0.0070, P=0.0155 and P=0.0018, respectively). There were no significant differences between the study groups in regards to the proportion of patients with sustained progression (P=0.209). Secondary: Not reported
Miller et al. ⁴⁷ (2008) GA 20 mg SC daily	OL, PRO Patients with RRMS	N=46 Up to 22 years	Primary: ARR, percentage of relapse-free patients, change in EDSS and adverse events Secondary: Not reported	Primary: Throughout the course of the study patients experienced a statistically significant reduction in the ARR from 2.9 to 0.1 at last observation (P<0.0001). Of patients who continued therapy through the end of the study 72% were free of relapses (P value not reported). There were no significant changes in the mean EDSS scores from baseline (P=0.076) with the majority (67%) of continuing patients exhibiting improved or stable EDSS scores. The most commonly reported adverse events were injection site reactions. Six patients who received GA for up to 22 years reported lipoatrophy. Skin necrosis was not observed. A discontinuation rate of 61% was observed. The most common reason for discontinuing the study was withdrawal of consent. Secondary: Not reported
La Mantia et al. ⁴⁸ (2010) GA 20 mg SC daily vs	MA RCTs comparing GA and placebo in patients of any age or gender with	N=1,458 (540 with RRMS) Up to 35 months	Primary: Patient disease progression (defined as worsening of at least one point in	Primary: Treatment with GA did not significantly reduce the risk of disease progression at two years (RR, 0.75; 95% CI, 0.51 to 1.12; P=0.16) or at 35 months (RR, 0.81; 95% CI, 0.50 to 1.29; P=0.37). Patients randomized to receive GA experienced small yet significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo</p>	<p>definite MS of any severity according to Poser criteria</p>		<p>EDSS for six months), mean changes in EDSS score, frequency of clinical relapses, patients who remained relapse-free, frequency of adverse events and quality of life</p> <p>Secondary: Number of patients requiring steroid courses, hospital admissions and length of stay</p>	<p>decreases in EDSS scores at two years (WMD, -0.33; 95% CI, -0.58 to -0.08; P=0.009) and at 35 months (WMD, -0.45; 95% CI, -0.77 to -0.13; P=0.006).</p> <p>Compared to placebo, there was a significant reduction in the frequency of clinical relapses reported with GA use at one year (-0.35; P=0.0002), at two years (-0.51; P=0.0006) and at 35 months (-0.64; P=0.002).</p> <p>Patients randomized to receive GA were more likely to remain relapse-free after one year of treatment compared to patients randomized to receive placebo (RR, 1.28; 95% CI, 1.02 to 1.62; P=0.03). The risk of being relapse-free after two years and 35 months continued to be higher in the GA treatment group, although the difference was not statistically significant (RR, 1.39; 95% CI, 0.99 to 1.94; P=0.06 and RR, 1.33; 95% CI, 0.86 to 2.06; P=0.19, at two years and 35 months, respectively).</p> <p>Injection-site reactions including itching, swelling, redness and pain occurred more frequently with GA compared to placebo (P<0.05 for all comparisons).</p> <p>Secondary: There was a significantly lower risk of requiring steroids in patients treated with GA compared to patients treated with placebo over nine months (RR, 0.65; 95% CI, 0.52 to 0.82; P=0.0002), although only one study evaluated this outcome.</p> <p>Data from hospital admission rates showed that patients receiving GA experienced fewer hospitalization by the end of follow-up compared to patients who were treated with placebo (RR, 0.54; 95% CI, 0.31 to 0.93; P=0.02).</p>
<p>Khan et al.⁴⁹ (2013) GALA</p> <p>GA 40 mg SC three times weekly</p>	<p>DB, MC, PC, PG, Phase III, RCT</p> <p>Patients 18 to 55 years of age with RRMS with at least 1 documented</p>	<p>N=1,404</p> <p>12 months</p>	<p>Primary: Total number of confirmed relapses during the 12-month PC phase</p> <p>Secondary:</p>	<p>Primary: GA group had a 34% reduction in the risk of relapse compared to placebo group (mean ARR, 0.331 vs 0.505; RR, 0.656; 95% CI, 0.539 to 0.799; P<0.0001).</p> <p>Secondary: The time to first confirmed relapse was significantly longer in the GA</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs placebo</p>	<p>relapse in the 12 months before screening, or at least 2 documented relapses in the 24 months before screening, and an EDSS score ≤ 5.5 with relapse-free for ≥ 30 days</p>		<p>Cumulative number of new/newly enlarging T2 lesions as months 6 and 12, cumulative number of Gd-enhancing lesions on T1-WI taken at months 6 and 12, brain atrophy defined as the percentage brain volume change from baseline to month 12, time to the first confirmed relapse, proportion of relapse-free patients, total number of severe confirmed relapses defined as those requiring hospitalizations or intravenous steroids</p>	<p>group compared to placebo group (393 days vs 377 days; HR, 0.606; 95% CI, 0.493 to 0.744; $P < 0.0001$).</p> <p>GA group (77.0%) compared to placebo group (65.5%) had a greater proportion of relapse-free patients (OR, 1.928; 95% CI, 1.491 to 2.494; $P < 0.0001$).</p> <p>GA group was associated with 35% reduction in annualized rate of severe relapse (0.301 vs 0.466; RR, 0.644; 95% CI, 0.526 to 0.790; $P < 0.0001$).</p> <p>Patients in the GA group experienced 45% reduction in the cumulative number of Gd-enhancing T1 lesions compared to placebo (RR, 0.552; 95% CI, 0.436 to 0.699; $P < 0.0001$) and 35% reduction in the cumulative number of new or newly enlarging T2 lesions (RR, 0.653; 95% CI, 0.546 to 0.780; $P < 0.0001$) at months 6 and 12.</p> <p>The percentage change in normalized brain volume at month 12 from baseline was similar between treatment arms (20.706 with GA group vs 20.645 with placebo group; $P = 0.2058$).</p> <p>The most common adverse reactions were injection-site reactions with 35.2% in the GA group vs 5.0% in the placebo group with 99.9% reactions being mild or moderate in severity. The most common injection-site reactions with an incidence of $> 5\%$ in the GA group were erythema (20.9%), injection site pain (10.4%) and pruritics (5.9%).</p> <p>Total number of severe confirmed relapses defined as those requiring hospitalizations or intravenous steroids results were not noted.</p>
<p>Carmona et al.⁵⁰ (2008)</p> <p>IFNβ-1b (Betaseron[®]) 0.25 mg SC every other day</p> <p>vs</p>	<p>OL, PRO</p> <p>Patients with clinically definite RRMS and a history of ≥ 2 relapses in the previous two years</p>	<p>N=159</p> <p>Up to 5 years</p>	<p>Primary: Percentage of relapse-free patients, ARR, time to first relapse, disability progression (assessed by change</p>	<p>Primary:</p> <p>The percentage of patients treated with IFNβ-1b who were relapse-free at the end of follow-up was 21.7% (P value not reported). At two years of follow-up, 32.5% of patients in the IFNβ-1b group were relapse-free compared to 22.7% of patients in the control group (P=NS).</p> <p>The mean ARR in the IFNβ-1b group was 0.70 relapses per year (P value not reported). The mean ARR at two year follow-up in the IFNβ-1b</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no treatment			<p>in EDSS scores) and time to progression</p> <p>Secondary: Not reported</p>	<p>group was 0.74 compared to 2.20 in the control group (P=0.001).</p> <p>The median time to first relapse in the IFNβ-1b group was 375 days compared to 313 days in the control group (P=0.26). The mean number of relapses after two years of treatment decreased by 47% (from 3.2 at baseline to 1.7; P value not reported).</p> <p>At 59 months of follow-up, 25% of IFNβ-1b treated patients progressed by one point on the EDSS from baseline (P value not reported). The mean time that it took for the IFNβ-1b treated patients to progress by one point on the EDSS was longer compared to the control group (72.94 vs 36.94 months; P=0.002).</p> <p>Higher EDSS scores were observed at the end of follow-up among patients who had experienced a relapse during the first 12 months of treatment compared to those patients who did not have a relapse (3.37 vs 2.36; P=0.003).</p> <p>At the end of follow-up, 70% of patients remained on IFNβ-1b therapy with sustained efficacy and good tolerance.</p> <p>Secondary: Not reported</p>
<p>PRISMS study group⁵¹ (1998)</p> <p>IFNβ-1a (Rebif[®]) 22 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Rebif[®]) 44 μg SC three times weekly</p>	<p>DB, I, MC, PC, RCT</p> <p>Adult patients, median age 34.9 years, with RRMS and EDSS scores 0 to 5 and \geq2 relapses in the preceding two years</p>	<p>N=560</p> <p>2 years</p>	<p>Primary: Mean number of relapses</p> <p>Secondary: Relapse rate, percentage of patients relapse-free at one and two years, mean number of moderate to severe relapses, mean number of hospital</p>	<p>Primary: Patients randomized to IFNβ-1a 22 and 44 μg groups experienced significantly fewer mean number of relapses compared to patients receiving placebo at two years of therapy (1.82 and 1.73 vs 2.56, respectively; P<0.005).</p> <p>Secondary: Compared to the placebo group, the relapse rate was reduced by 29% in the IFNβ-1a 22 μg group and 32% in the IFNβ-1a 44 μg group (P value not reported).</p> <p>At one year, a significantly greater percentage of patients in the IFNβ-1a 22 and 44 μg groups were relapse-free compared to those receiving placebo (37 and 45 vs 22%, respectively; P<0.005).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs placebo</p>			<p>admissions, mean change in EDSS, median time to first relapse, time to sustained progression, burden of disease and adverse events</p>	<p>At two years, a significantly greater percentage of patients in the IFNβ-1a 22 μg (27 vs 16%; P≤0.05) and IFNβ-1a 44 μg (32 vs 16%; P<0.005) groups were relapse-free compared to those receiving placebo.</p> <p>The mean number of moderate to severe relapses was significantly lower in the IFNβ-1a 22 and 44 μg groups compared to the placebo group (0.71 and 0.62 vs 0.99; P<0.005).</p> <p>The mean number of hospital admissions was significantly lower in the IFNβ-1a 44 μg group compared to patients receiving placebo (0.25 vs 0.48, respectively; P<0.005).</p> <p>The mean change in EDSS was significantly smaller in the IFNβ-1a 22 and 44 μg groups compared to patients receiving placebo (0.23 and 0.24 vs 0.48, respectively; P≤0.05).</p> <p>The median time to first relapse was delayed by three and five months in the IFNβ-1a 22 and 44 μg groups, respectively (P value not reported).</p> <p>The time to sustained progression was significantly longer in both the IFNβ-1a 22 and 44 μg groups compared to the placebo group (P<0.05).</p> <p>The burden of disease was significantly increased in the placebo group compared to the IFNβ-1a 22 and 44 μg groups (10.9 vs -1.2 and -3.8%, respectively; P<0.0001 for both compared to placebo).</p> <p>The following adverse events occurred more frequency with IFNβ-1a treatment compared to placebo: injection-site reactions, lymphopenia, increased ALT, leukopenia and granulocytopenia (P≤0.05).</p>
<p>Kappos et al.⁵² (2006) PRISMS IFNβ-1a (Rebif®) 22 μg SC three times weekly</p>	<p>DB, ES, I, PC, RCT This was a PRISMS extension study; patients with RRMS and EDSS</p>	<p>N=382 Up to 8 years</p>	<p>Primary: Mean change in EDSS scores, progression to SPMS, ARR, percentage of relapse-free</p>	<p>Primary: Among patients returning for follow-up after eight years of therapy, mean EDSS scores increased by 1.1 points. Approximately 31.3% of patients progressed by two EDSS points. The longest time to reach disability progression was observed among patients initially randomized to IFNβ-1a 44 μg (2.3 vs 1.0 year for the late treatment group).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>IFNβ-1a (Rebif®) 44 μg SC three times weekly</p> <p>vs</p> <p>placebo for initial two years, followed by IFNβ-1a 22 or 44 μg (Rebif®) SC three times a week for additional six years (later treatment group)</p>	<p>scores 0 to 5 and ≥2 relapses within two years prior to study onset</p>		<p>patients, annualized change in T2 burden of disease, change in brain parenchymal volume, adverse events and antibody development</p> <p>Secondary: Not reported</p>	<p>Progression to SPMS occurred in 19.7% of patients. The time to developing SPMS was 5.3 years.</p> <p>The ARR was lower in the IFNβ-1a 44 μg (0.60 vs 0.78; P=0.014) and IFNβ-1a 22 μg (0.63 vs 0.78; P<0.001) treatment groups compared to patients in the late treatment group.</p> <p>The greatest percentage of patients remaining relapse-free at follow-up were those receiving IFNβ-1a 44 μg (15.4%) compared to patients in the IFNβ-1a 22 μg (8.1%) and late treatment groups (6.5%; P value not reported).</p> <p>Compared to the late treatment group, patients initially randomized to IFNβ-1a 44 μg therapy had a lower increase in T2 burden of disease (5.0 vs 24.5%; P=0.002).</p> <p>At two years of follow-up, patients receiving placebo experienced a greater median annualized increase in T2 burden of disease compared to the IFNβ-1a 22 and 44 μg groups (6.5 vs -0.7 and -2.8%, respectively; P value not reported).</p> <p>At eight-year follow-up, all treatment groups experienced a median relative reduction in brain parenchymal volume of 3.9% from baseline (P value not reported).</p> <p>At eight-year follow-up, the most frequently reported adverse events were injection-site disorders, reported by 44% of patients. Flu-like symptoms occurred in 11.7% of patients. Elevated ALT was the most common liver abnormality, affecting approximately 8.4% of patients on IFNβ-1a therapy. Lymphopenia and leukopenia were reported by 19.6 and 14.0% of patients receiving IFNβ-1a therapy, respectively.</p> <p>Of patients who developed antibodies, 90% did so during the first two years of therapy.</p> <p>Of patients returning for follow-up after eight years of therapy 72% remained on SC IFNβ-1a.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Rice et al.⁵³ (2009)</p> <p>IFNα-2a (Roferon-A[®]) 9 MIU IM every other day</p> <p>vs</p> <p>IFNβ-1a (Avonex[®]) 6 to 12 MIU IM once-weekly</p> <p>vs</p> <p>IFNβ-1a (Rebif[®]) 6 to 12 MIU SC three times weekly</p> <p>vs</p> <p>IFNβ-1b (Betaseron[®]) 0.6 to 8 MIU SC every other day</p> <p>vs</p> <p>placebo</p>	<p>MA</p> <p>DB, PC, RCTs of patients with RRMS who were treated with recombinant IFN, given by the SC or the IM route</p>	<p>N=1,301 (8 studies)</p> <p>Up to 24 months</p>	<p>Primary:</p> <p>Exacerbation rate during treatment and follow-up, percent of patients who progressed during treatment, mean change in EDSS score and the percent of patients unable to walk without aid at the end of treatment (EDSS >5.5)</p> <p>Secondary:</p> <p>Time to first exacerbation, time to progression in disability, percent of patients requiring steroid administration during IFN treatment and follow-up, hospitalizations during treatment and follow-up, number of patients reporting adverse events, mean change of total lesion load on T2</p>	<p>Secondary:</p> <p>Not reported</p> <p>Primary:</p> <p>Patients treated with IFN therapy were significantly less likely to experience an exacerbation during the first year of treatment compared to patients receiving placebo (pooled RR, 0.73; 95% CI, 0.55 to 0.97; P=0.03). During the first two years, IFN treatment was associated with lower rates of exacerbations compared to placebo (55 vs 69%; RR, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The type of IFN administered or route of administration did not appear to affect the number of patients experiencing exacerbations.</p> <p>Disease progression, defined as ≥ 1 EDSS point increase for three to six months, occurred in 20% of the patients receiving IFN treatment compared to 29% of patients receiving placebo over two years (RR, 0.69; 95%CI, 0.55 to 0.87; P=0.002).</p> <p>Patients treated with IFN experienced a small but significant decrease in EDSS score relative to patients treated with placebo (WMD, -0.25; 95% CI, -0.05 to -0.46; P=0.01). Notably, this outcome was only reported in two studies.</p> <p>No data was available for the number of patients who were unable to walk without aid.</p> <p>Secondary:</p> <p>The frequency of steroid administration over the first year of treatment was only reported in two studies. Result from one study found a non-significant reduction in steroid requirements between IFN treatment and placebo, while the second study reported no difference between treatments. One study evaluated steroid requirements over two years and concluded that patients treated with IFN were less likely to require steroid administration compared to patients treated with placebo (RR, 0.70; 95% CI, 0.56 to 0.87; P=0.001).</p> <p>There was no reduction in the frequency of hospitalization between</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>weighted images, and the number of patients continuing to show gadolinium-enhancing lesions during treatment and follow-up</p>	<p>participants treated with IFN and those treated with placebo (RR, 0.44; 95% CI, 0.08 to 2.36; P=0.30). Flu-like symptoms, injection site reactions, development of psychiatric disorders, leukopenia, lymphopenia and elevated liver enzymes were all reported more frequently in IFN groups compared to the placebo group (P<0.05 for all).</p> <p>The evolution in MRI technology in the decade in which these studies were conducted and varied data reporting in the studies made it impossible to perform a quantitative analysis of the MRI results. A reduction in gadolinium enhancing lesions was apparent after one year of treatment in two studies, but the benefit was not apparent at two years.</p> <p>No data were available for the time to first exacerbation or time to progression in disability.</p>
<p>Freedman et al.⁵⁴ (2008)</p> <p>GA 20 mg SC weekly</p> <p>vs</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1a (Rebif®) 22 to 44 µg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 µg IM once-weekly</p>	<p>MA</p> <p>DB, MC, PC, RCTs with a sample size >30 patients, that included patients at least 18 years of age diagnosed with a clinically-definite RRMS</p>	<p>N=2,351 (6 studies)</p> <p>Up to 2 years</p>	<p>Primary:</p> <p>The proportion of patients relapse-free at one year, proportion of patients relapse-free at two years, proportion of patients progression-free at two years, proportion of patients free of gadolinium-enhancing lesions at one year</p> <p>Secondary:</p> <p>Not reported</p>	<p>Primary:</p> <p>Compared to placebo, a significantly greater proportion of patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.23; 95% CI, 0.14 to 0.33; P value not reported) and natalizumab were relapse-free at one year (AAR, 0.23; 95% CI, 0.17 to 0.30; P value not reported). The proportion of patients receiving IFNβ-1a 30 µg IM or GA that were relapse-free at one year of therapy was not statistically different from those receiving placebo (P value not reported).</p> <p>Compared to placebo, a significantly greater proportion of patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.17; 95% CI, 0.09 to 0.26; P value not reported), IFNβ-1b (AAR, 0.14; 95% CI, 0.04 to 0.25; P value not reported), and natalizumab were relapse-free at two years (AAR, 0.26; 95% CI, 0.20 to 0.33; P value not reported). The proportion of patients receiving GA who were relapse-free at two years of therapy was not statistically different from those receiving placebo (P value not reported).</p> <p>Compared to placebo, a significantly greater proportion of patients were progression-free at two years among patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.11; 95% CI, 0.01 to 0.20; P value not reported), IFNβ-1a 30 µg IM (AAR, 0.13; 95% CI, 0.03 to 0.23; P value not reported) and natalizumab (AAR, 0.12; 95% CI, 0.06 to 0.18; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs natalizumab 300 mg IV infusion every four weeks vs placebo</p>				<p>The proportion of patients progression-free at two years among patients receiving IFNβ-1b or GA was not statistically different from those receiving placebo (P value not reported).</p> <p>Compared to placebo, a significantly greater proportion of patients were free of gadolinium-enhancing lesions at one year among patients receiving IFNβ-1a 22 to 44 μg SC (AAR, 0.31; 95% CI, 0.17 to 0.44; P value not reported), IFNβ-1a 30 μg IM (AAR, 0.12; 95% CI, 0.01 to 0.24; P value not reported) and natalizumab (AAR, 0.28; 95% CI, 0.23 to 0.33; P value not reported). The proportion of patients free of gadolinium-enhancing lesions at one year among patients receiving GA was not statistically different from patients receiving placebo (P value not reported).</p> <p>Secondary: Not reported</p>
<p>Coppola et al.⁵⁵ (2006) IFNβ-1a (Avonex®) 30 μg IM once-weekly</p>	<p>OS, PRO Patients with a clinically definite or laboratory-confirmed MS</p>	<p>N=255 Mean of 31.7 months</p>	<p>Primary: Percentage of patients progression-free, percentage of patients relapse-free, relapse rate, change in EDSS scores and estimated time to disability progression Secondary: Not reported</p>	<p>Primary: At three years of therapy, 58% of patients remained progression-free, and 39.6% of patients remained relapse-free (P values not reported).</p> <p>At three years of therapy, 88% of patients had an improved relapse rate compared to baseline (P value not reported).</p> <p>After three years of therapy, mean EDSS scores increased by 0.4 points from baseline (P value not reported). The estimated median time to disability progression among patients receiving IFNβ-1a therapy was 4.5 years (P value not reported).</p> <p>Within the three-year follow-up period, 31% of patients discontinued the study. Reasons for discontinuation were disease activity (66%), voluntary decision (23%) and adverse events (11%).</p> <p>Secondary: Not reported</p>
<p>Polman et al.⁵⁶ (2006) AFFIRM</p>	<p>DB, RCT Patients 18 to 50</p>	<p>N=942 ≥2 years</p>	<p>Primary: Rate of clinical relapse at one year,</p>	<p>Primary: After one year of treatment, natalizumab reduced the annualized rate of relapse to 0.26 relapse per year, as compared with 0.81 relapse per year</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Natalizumab vs placebo</p>	<p>years of age with a diagnosis of relapsing MS who had a score of 0 to 5.0 on the EDSS scale who had undergone MRI showing lesions consistent with MS, who had had at least one medically documented relapse within the 12 months before the study began</p>		<p>cumulative probability of sustained progression of disability at two years</p> <p>Secondary: Number of new or enlarging hyperintense lesions as detected by T2-weighted MRI, the number of lesions as detected by gadolinium-enhanced MRI, and the proportion of relapse-free patients</p>	<p>in the placebo group (P<0.001). The 68% relative reduction in the annualized rate of relapse produced by natalizumab was maintained at two years (P<0.001). Subgroup and sensitivity analyses showed results consistent with the primary analysis.</p> <p>A sustained progression of disability over two years was significantly less likely in the natalizumab group than in the placebo group. At two years, the cumulative probability of progression (on the basis of Kaplan–Meier analysis) was 17% in the natalizumab group and 29% in the placebo group (HR, 0.58; 95% CI, 0.43 to 0.77; P<0.001).</p> <p>Secondary: The proportion of relapse-free patients was significantly higher in the natalizumab group than in the placebo group at one year (77 vs 56%, P<0.001) and at two years (67 vs 41%, P<0.001). Natalizumab reduced the mean number of new or enlarging hyperintense lesions detected by T2-weighted MRI over two years by 83%, as compared with placebo (P<0.001). Over two years, no new or enlarging hyperintense lesions developed in 57% of patients in the natalizumab group, as compared with 15% of patients in the placebo group. In contrast, 68% of patients in the placebo group had at least three new or enlarging hyperintense lesions, as compared with only 18% of patients in the natalizumab group. Natalizumab reduced the mean number of lesions as detected by gadolinium-enhanced MRI by 92% as compared with placebo at both one year and two years (P<0.001). In addition, lesions detected by gadolinium-enhanced MRI were absent in 97% of patients in the natalizumab group as compared with 72% of patients in the placebo group on MRI scanning at two years.</p>
<p>Lublin et al.⁵⁷ (2014) Natalizumab vs placebo</p>	<p>PH of AFFIRM study</p> <p>Adult patients (18 to 50 years of age) with a diagnosis of RRMS, who had a score of 0.0 to 5.0 on the EDSS,</p>	<p>N=283</p> <p>Up to 120 weeks</p>	<p>Primary: 1) Relapse clinical severity, defined as the change in EDSS score between pre-relapse and at-relapse assessments; 2) Relapse-induced</p>	<p>Primary: At relapse, an increase in EDSS score of ≥ 0.5 points was seen in 71% of natalizumab patients and 84% of placebo (P=0.0088), while an increase of ≥ 1.0 point was seen in 49% of natalizumab patients and 61% of placebo (P=0.0349). Treatment effects on the clinical severity of relapses were most apparent in patients with baseline EDSS score <3.0. In this subgroup, 74% of natalizumab versus 91% of placebo patients experienced an increase in EDSS score of ≥ 0.5 points at first relapse assessment (P=0.0019), while 50% of natalizumab versus 71% of</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	<p>cranial MRI showing lesions consistent with MS, and at least one medically documented relapse within the 12 months before the baseline visit</p>		<p>residual disability, defined as the change in EDSS score between pre-relapse and post-relapse assessments; 3) Probability of 12-week and 24-week confirmed complete EDSS recovery from disabling relapses</p> <p>Secondary: Not reported</p>	<p>placebo patients showed an increase of ≥ 1.0 point ($P=0.0048$). Among those with baseline EDSS score ≥ 3.0, there was no significant difference between the percentage of natalizumab and placebo patients who experienced an increase in EDSS of either 0.5 (natalizumab, 68%; placebo, 70%; $P=0.8259$) or 1.0 point (natalizumab, 48%; placebo, 43%; $P=0.5976$) at relapse.</p> <p>Residual disability (≥ 0.5-point increase in EDSS from pre- to post-relapse) remained in 31% and 45% of patients in the natalizumab and placebo groups, respectively ($P=0.0136$). A significant difference was observed among those with a baseline EDSS score < 3.0; 33% of those who received natalizumab showed a pre- to post-relapse residual EDSS increase of ≥ 0.5 points versus 47% of those given placebo ($P=0.0478$). The difference was not significant in relapse-induced residual EDSS impairment between natalizumab and placebo patients with a baseline EDSS score ≥ 3.0 (natalizumab, 29%; placebo, 40%; $P=0.1930$).</p> <p>In patients with an increase in EDSS of ≥ 0.5 points during relapse, natalizumab increased the cumulative probability of 12-week and 24-week confirmed complete recovery from relapse by 55% (HR, 1.554; 95% CI, 1.085 to 2.226; $P=0.0161$) and 61% (HR, 1.609; 95% CI, 1.066 to 2.430; $P=0.0236$) relative to placebo, respectively. In patients with an increase in EDSS of ≥ 1.0 point during relapse, natalizumab increased the cumulative probability of 12-week and 24-week confirmed complete recovery from relapse by 67% (HR, 1.673; 95% CI, 1.046 to 2.678; $P=0.0319$) and 66% (HR, 1.656; 95% CI, 0.968 to 2.832; $P=0.0655$) relative to placebo, respectively.</p> <p>Secondary: Not reported</p>
<p>Fox et al.⁵⁸ (2014) RESTORE</p> <p>Natalizumab vs</p>	<p>MC, PG, RCT</p> <p>Patients 18 to 60 years of age with relapsing MS who were relapse-free for one year on</p>	<p>N=175</p> <p>52 weeks</p>	<p>Primary: Radiographic and clinical disease activity in patients with MS undergoing up to a 24-week</p>	<p>Primary: During the randomized treatment period, 49 of 122 patients (40%) randomized to placebo or other therapies had MRI activity meeting disease recurrence criteria, while none of the patients randomized to natalizumab had MRI activity meeting the criteria ($P<0.001$). Thirty-four percent (23/68) of patients with high disease activity prior to natalizumab treatment had MRI activity meeting criteria during the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>placebo</p> <p>vs</p> <p>alternate immunomodulatory therapy (IM interferon β-1a [Avonex[®]], glatiramer acetate [Copaxone[®]], or methylprednisolone)</p>	<p>natalizumab therapy</p>		<p>interruption of natalizumab therapy</p> <p>Secondary: Not reported</p>	<p>randomized treatment period; the proportion was 26% (26/99) for those with low disease activity prior to natalizumab treatment (P=0.305). No MRI activity meeting defined disease recurrence criteria was detected prior to week 12. A total of 49 patients developed MRI findings that met defined criteria for disease recurrence; three patients (6%) at week 12, 37 patients (76%) at week 16 or 20, and nine patients (18%) after week 20.</p> <p>Twenty-three of 122 patients (19%) off natalizumab and 2 of 45 patients (4%) on natalizumab experienced relapses during the randomized treatment period (P=0.026). Relapses occurred in 21% (14/68) of patients with high disease activity and in 11% (11/99) of patients with low disease activity prior to starting natalizumab (P=0.122). Of 25 relapses occurring during the randomized treatment period, two (8%) occurred between weeks four and eight, nine (44%) occurred between weeks eight and 16, and 14 (56%) occurred between weeks 16 and 28. Two patients with high disease activity (in glatiramer and methylprednisolone groups) experienced a relapse in both the randomized treatment period and in the follow-up period.</p> <p>Secondary: Not reported</p>
<p>Outteryck et al.⁵⁹ (2014) BIONAT Natalizumab</p>	<p>Cohort, MC, PRO</p> <p>Patients with relapsing–remitting MS starting natalizumab therapy at 18 MS centres in France since June 2007 were included and were followed prospectively</p>	<p>N=793</p> <p>≥2 years</p>	<p>Primary: Clinical and radiological response to natalizumab after 2 years of treatment</p> <p>Secondary: Not reported</p>	<p>Primary: Natalizumab was discontinued in 17.78% of patients. The most frequent causes, together representing more than half the discontinuations, were pregnancy planning (24.82%), cutaneous allergy (17.02%), always occurring in the first year, conversion to a secondary progressive form of MS (12.06%) and serious adverse event (8.51%). The proportion of patients without combined disease activity was 45.59% during the first two successive years of treatment. Systematic dosage of anti-natalizumab antibodies detected only two supplementary patients with anti-natalizumab antibodies compared with strict application of recommendations. A significant decrease of IgG and IgM concentrations at two years of treatment was found.</p> <p>Secondary: Not reported</p>
<p>Rudick et al.⁶⁰</p>	<p>DB, PC, PG, RCT</p>	<p>N=1,171</p>	<p>Primary:</p>	<p><i>SENTINEL</i> was stopped approximately one month early because of two</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2006) SENTINEL</p> <p>Natalizumab added to interferon β-1a (Avonex®)</p> <p>vs</p> <p>interferon β-1a (Avonex®) alone</p>	<p>Patients were 18 to 55 years of age; had a diagnosis of relapsing–remitting multiple sclerosis, a score on the EDSS (possible scores range from 0 to 10, with higher scores indicating more severe disease) between 0 and 5.0, and a MRI scan revealing lesions consistent with a diagnosis of MS; had received treatment with interferon beta-1a for at least 12 months before randomization; and had had at least one relapse during the 12-month period before randomization</p>	<p>≥116 weeks</p>	<p>Rate of clinical relapse at one year; cumulative probability of sustained disability progression at two years</p> <p>Secondary: Number of new or enlarging T2-hyperintense lesions, the number of gadolinium-enhancing lesions, and the proportion of patients free of relapse</p>	<p>reports of progressive multifocal leukoencephalopathy (PML).</p> <p>Primary: Combination therapy reduced the annualized rate of relapse at one year, which was 0.82 with interferon beta-1a alone, compared to 0.38 (P<0.001) — a 54% reduction.</p> <p>Kaplan–Meier estimates of the cumulative probability of sustained disability progression at two years were 23% with combination therapy and 29% with interferon β-1a alone. Combination therapy resulted in a 24% decrease in the risk of sustained disability progression (HR, 0.76; 95% CI, 0.61 to 0.96; P=0.02). In the sensitivity analysis of the risk of disability progression sustained for 24 weeks, estimates of the cumulative probability of progression by two years were 15% for combination therapy and 18% for interferon β-1a alone (representing an 18% reduction with combination therapy); however, this difference was not statistically significant (P=0.17).</p> <p>Secondary: The number of new or enlarging T2-hyperintense lesions over the two-year period was reduced from 5.4 with interferon β-1a alone to 0.9 with combination therapy (P<0.001), representing an 83% reduction with combination therapy. The mean number of gadolinium-enhancing lesions at two years was 0.9 with interferon β-1a alone and 0.1 with combination therapy, representing an 89% reduction (P<0.001).</p> <p>The proportion of patients who were relapse-free at two years was 54% in the combination-therapy group, as compared with 32% in the group assigned to interferon β-1a alone (P<0.001). The risk of relapse was 50% lower with combination therapy (HR, 0.50; 95% CI, 0.43 to 0.59; P<0.001).</p>
<p>Kalincik et al.⁶¹ (2015)</p> <p>Natalizumab</p> <p>vs</p>	<p>OBS, PRO</p> <p>Patients with relapsing–remitting MS in the MSBase registry who had</p>	<p>N=792</p> <p>12 months</p>	<p>Primary: Relapse (defined as occurrence of new symptoms or exacerbation of existing symptoms</p>	<p>Primary: Treatment persistence following the baseline did not differ between the compared therapies, with the proportion of patients discontinuing therapy at 24 months reaching 27% and 31% in the natalizumab and fingolimod groups, respectively (P=0.9). The proportion of relapse-free patients was higher among those switching to natalizumab than fingolimod (HR, 1.5;</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fingolimod	switched therapy from interferon β or glatiramer acetate to either natalizumab or fingolimod (treatment gap < 3 months; no unified escalation protocol was used) after on-treatment relapse and/or progression of disability documented within the preceding six months (i.e., clinical breakthrough activity)		persisting for at least 24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse), Progression of EDSS (defined as increase of ≥ 1 EDSS step (≥ 1.5 EDSS steps if baseline EDSS was 0) sustained for ≥ 6 months), ARR Secondary: Not reported	95% CI, 1.1 to 2.2; P=0.02), and the cumulative hazard of relapses was relatively lower in the natalizumab group (HR, 0.6; 95% CI, 0.4 to 0.8, P=0.002). ARR decreased in both groups, with a more prominent drop after switching to natalizumab (1.5 to 0.2) compared to fingolimod (1.3 to 0.4; P=0.002). The difference in ARR was sustained throughout the two years post-switch. Secondary: Not reported
O'Connor et al. ⁶² (2011) TEMSO Teriflunomide 7 mg QD vs teriflunomide 14 mg QD vs placebo	DB, MC, PC, PG, RCT Patients aged 18 to 55 years who met McDonald criteria for MS diagnosis and had relapsing clinical course with or without progression, EDSS score ≤ 5.5 and 1 relapse in previous year or 2 relapses in previous 2 years	N=1,088 108 weeks	Primary: ARR Secondary: Disability progression, change in total MRI lesion volume from baseline	Primary: ARR was significantly reduced in both teriflunomide 7 mg (0.37; CI, 0.32 to 0.43) and 14 mg groups (0.37; CI, 0.31 to 0.44) compared to placebo (0.54; CI 0.47 to 0.62; P<0.001 for both). This represented a RRR of 16.7% and 31.2%, respectively. Secondary: The percentage of patients with confirmed progression of disability in the 14 mg group (20.2%; CI, 15.6 to 24.7) was marginally lower than the placebo group (27.3%; CI, 22.3 to 32.3; P=0.03). The percentage of patients with confirmed progression of disability was not significantly different than placebo in the 7 mg group. The changes in total MRI brain lesion volume from baseline were reduced in both the 7 mg group (1.31 \pm 6.80 mL) and the 14 mg group (0.72 \pm 7.59 mL) compared to the placebo group (2.21 \pm 7.00 mL; P=0.03 and P<0.001, respectively).
O'Connor et al. ⁶³	DB, ES, MC	N=742	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2016) TEMSO Extension Teriflunomide 7 mg QD vs placebo/teriflunomide 7 mg QD vs teriflunomide 14 mg QD vs placebo/teriflunomide 14 mg QD</p>	<p>Patients who completed TEMSO entered the long-term extension and patients originally receiving placebo were re-randomized to teriflunomide 7 mg or 14 mg, while patients receiving active treatment continued on the original dose</p>	<p>Up to 9 years</p>	<p>Long-term safety Secondary: Long-term efficacy</p>	<p>Over the extension, approximately 90% of patients reported at least one adverse event. The majority (~80%) of patients who entered the extension experienced an adverse event in extension year one. The most commonly reported adverse events in the extension were nasopharyngitis, headache, and alanine aminotransferase (ALT) increase. Serious adverse events were evenly distributed across groups, with no evidence of a dose effect. Adverse events leading to discontinuation were reported in 82 patients (11% of the study population) without a dose effect. The most common reason for discontinuation was confirmed ALT increase, which was required by protocol for ALT elevations >3x upper limit of normal confirmed by a repeated measurement. Other adverse events leading to discontinuation were relatively infrequent. Generally, for each individual adverse event, the number of episodes per patient was low (≤ 2.0) and similar across teriflunomide groups.</p> <p>Secondary: There was a noticeable drop in ARR for the group of patients who received placebo in the core study as they switched to teriflunomide in the extension. ARRs declined over the extension and were numerically lower at the cutoff date than at the end of the core study in all treatment groups. The ARR for the combined core plus extension study periods was lower in patients who received teriflunomide throughout compared with those who began teriflunomide 7 mg after 108 weeks of placebo treatment (14-mg/14-mg group, $p=0.003$; 7-mg/7-mg group, $P=0.022$). There was a similar (albeit nonsignificant) effect for patients who received teriflunomide throughout compared with the placebo/14-mg group. Regardless of their dose allocation, $\geq 55\%$ of patients did not experience a relapse in the extension. Disability remained stable in all treatment groups (median EDSS score ≤ 2.5; probability of 12-week disability progression ≤ 0.48).</p>
<p>Freedman et al.⁶⁴ (2012) Teriflunomide 7 mg vs</p>	<p>DB, MC, PC, RCT, ES Patients aged 18 to 55 years who met McDonald criteria for MS diagnosis</p>	<p>N=118 24 weeks N=86 24 week</p>	<p>Primary: Safety and tolerability Secondary: ARR, total number T1-gadolinium-</p>	<p>Primary: The overall incidence of patients experiencing at least one TEAE was similar across all groups (placebo: 85.4%; teriflunomide 7 mg: 89.2%; teriflunomide 14 mg: 84.2%). TEAEs occurring more frequently in the teriflunomide groups (incidence $\geq 10\%$) in any group were increased ALT/AST, decreased white blood cells counts, nasopharyngitis, fatigue, nausea and hypertension. The number of patients experiencing serious</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>teriflunomide 14 mg vs placebo</p> <p>All patients received IFNβ (Avonex® [IFNβ-1a] 30 μg IM QW or Rebif® [IFNβ-1a] 22 μg or 44 μg SC TIW or Betaseron® [IFNβ-1b] 0.25 mg SC QOD)</p>	<p>and had relapsing clinical course with or without progression, EDSS score ≤5.5 and had received a stable dose of IFNβ for 26 weeks before screening</p> <p>After initial randomization and treatment for 24 weeks, patients could enter the 24 week blinded extension study in which patients remained on their initial treatment regimen</p>	<p>extension</p>	<p>enhancing lesions, total T1-gadolinium-enhancing lesion volume per MRI scan</p>	<p>TEAEs during the initial 24 week study was similar across groups (placebo: 1; 7 mg: 2; 14 mg: 0), but the incidence was slightly higher in the 7 mg group during the 24 week extension study (placebo: 4.9%; 7 mg: 10.8%; 14 mg: 2.6%). Discontinuation due to TEAEs was low and similar across all groups. No deaths occurred during 48 weeks.</p> <p>Secondary: ARRs at 24 weeks and 48 weeks were not significantly different between groups.</p> <p>At baseline, 21.7% of patients had at least one T1-gadolinium-enhancing lesion. The total number of T1-gadolinium-enhancing lesions per MRI scan during the initial 24 week study was decreased in the teriflunomide groups, corresponding to a RRR compared to placebo of 82.6% (P=0.0009) for 7 mg and 84.4% (P=0.0001) for 14 mg. These RRRs were maintained at 48 weeks.</p> <p>Total T1-gadolinium-enhancing lesion volume per MRI scan was reduced in the teriflunomide groups, but only the 14 mg group reached a significant RRR at 24 weeks (7 mg: 67.6%, P=0.19; 14 mg: 64.7%, P=0.007). These reductions were maintained at 48 weeks.</p>
<p>Confavreux et al.⁶⁵ (2012)</p> <p>Teriflunomide 7 mg vs teriflunomide 14 mg</p>	<p>ES, OL</p> <p>Patients aged 18 to 65 years with RRMS, a EDSS ≤6 and at least two clinical relapses in the previous three years and one during the preceding year</p>	<p>N=147 0.05 to 8.5 years</p>	<p>Primary: Long-term safety</p> <p>Secondary: Relapses, EDSS, T2 lesion volume, cerebral volume</p>	<p>Primary: The most commonly reported treatment emergent adverse events included infections, hepatic disorders, gastrointestinal disorders, neurological disorders, psychiatric disorders and hematologic disorders. The incidence of serious adverse events was slightly higher in the 7 mg group (35.8%) than the 14 mg group (28.8%) and included increased hepatic enzymes, loss of consciousness, neutropenia, pneumonia, MS relapse and breast cancer (No P values reported). The proportion of patients who discontinued treatment to due to an adverse event was 13.6% in both the 7 and 14 mg groups. One death due to a sudden cardiac disorder was reported in a patient who had been taking teriflunomide 14 mg for 4.8 years. This death was not directly attributed to the study drug.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>The AARs decreased over time in the 7 and 14 mg groups and were 0.279 and 0.200 overall, respectively. The mean change (SD) in EDSS from baseline were 0.50 (1.29) and 0.34 (1.20), respectively (No P values reported).</p> <p>Mean cerebral volume decreased slightly more in the 7 mg group than in the 14 mg group at the end of the study. Mean (SD) percentage change from baseline in T2 volume was 62.66 (84.84)% and 72.28 (99.13)% in the 7 mg and 14 mg groups, respectively No P values reported).</p>
<p>Fox et al.⁶⁶ (2012) CONFIRM</p> <p>Dimethyl fumarate 240 mg BID</p> <p>vs</p> <p>dimethyl fumarate 240 mg TID</p> <p>vs</p> <p>GA 20 mg QD</p> <p>vs</p> <p>placebo</p> <p>The glatiramer acetate group was not an active comparator, but used as a referenced group. Patients receiving glatiramer were not blinded to treatment</p>	<p>DB, MC, PC, RCT</p> <p>Patients aged 18 to 55 years with a diagnosis of RRMS, an EDSS score of 0 to 5, and at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization</p>	<p>N=1,430</p> <p>96 weeks</p>	<p>Primary: ARR over two years</p> <p>Secondary: Number of new or enlarging hyperintense T2 lesions, number of new hypointense T1 lesions, proportion of patients with a relapse, time to disability progression</p>	<p>Primary: The ARR in patients receiving dimethyl fumarate twice daily and three times daily was 0.22 and 0.20, respectively. This corresponded to a reduction relative to placebo of 44% and 51% (P<0.001 for both).</p> <p>GAr was associated with a relative ARR reduction of 29% compared to placebo (P=0.001).</p> <p>Secondary: Dimethyl fumarate twice daily, three times daily and GA reduced the number of T2 lesions by 71%, 73% and 54%, respectively (all P<0.001 compared to placebo). The number of T1 lesions was reduced by 57% (P<0.001), 65% (P<0.001) and 41% (P=0.002) relative to placebo, respectively.</p> <p>Compared to placebo, dimethyl fumarate twice daily, three times daily and GA significantly reduced the risk of relapse by 34% (P=0.002), 45% (P<0.001) and 29% (P<0.01), respectively. However, disability progression was not significantly reduced in any group compared to placebo.</p> <p>Post hoc analysis directly comparing dimethyl fumarate twice daily and three times daily to glatiramer determined that a comparison of ARR resulted in P values of 0.10 and 0.02, respectively favoring dimethyl fumarate.</p> <p>The overall incidence of adverse events, serious adverse events and adverse events leading to discontinuation was similar in all groups. The</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
regimen.				most common adverse events reported in patients receiving dimethyl fumarate were flushing, gastrointestinal events, upper respiratory tract infections and erythema.
Castelli-Haley et al. ⁶⁷ (2008) GA SC vs IFNβ-1a (Rebif®) SC Doses not reported for either treatment arm.	CE, RETRO Patients (mean age 43) diagnosed with MS, with a procedure code, or outpatient prescription for GA or IFNβ-1a, and insurance coverage starting at least six months before and extending through 24 months after the index date; in addition, a continuous use cohort could not have used other disease-modifying therapy within the study period and were required to have received the study medication within 28 days of study end	N=845 (ITT); N=410 (continuous use) 24 months	Primary: Costs (direct medical costs, including inpatient, outpatient and prescription drug cost) and relapse rate (defined as hospitalization with an MS diagnosis or a seven-day steroid therapy) Secondary: Not reported	Primary: Compared to IFNβ-1a therapy, patients in the ITT cohort receiving GA experienced a significantly lower two-year relapse rate (5.92 vs 10.89%; P=0.0305). Compared to IFNβ-1a therapy, patients in the continuous use cohort receiving GA experienced a significantly lower two-year relapse rate (1.94 vs 9.09%; P=0.0049). Compared to IFNβ-1a therapy, patients in the ITT cohort receiving GA had significantly lower two-year estimated direct medical expenses (\$41,786 vs \$49,030; P=0.0002). Compared to IFNβ-1a therapy, patients in the continuous use cohort receiving GA had significantly lower two-year estimated direct medical expenses (\$45,213 vs \$57,311; P=0.0001). Secondary: Not reported
Cadavid et al. ⁶⁸ (2009) BECOME GA 20 mg SC daily vs	DB, MC, OL, PG, RCT Treatment-naïve patients with RRMS or clinically isolated syndrome	N=75 24 months	Primary: Number of combined active lesions per patient per scan during year one, combined active lesions	Primary: The median number of combined active lesions per patient per scan during year one was not significantly different between patients receiving treatment with GA or IFNβ-1b (0.58 vs 0.63, respectively; P=0.58). Moreover, the number of patients who were active-lesion-free during the first year was similar among GA and IFNβ-1b-treated patients (19 vs 26%, respectively; P=0.59).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p>	<p>suggestive of MS</p>		<p>includes all enhancing lesions and nonenhancing new T2/fluid-attenuated inversion recovery lesions</p> <p>Secondary: Number of new lesions and clinical relapses over two years</p>	<p>Secondary: Over 24 months, the number of new lesions per patient per month was lower with GA compared to IFNβ-1b, but did not reach statistical significance (0.23 vs 0.46; P=0.13).</p> <p>The total number of relapses between GA and IFNβ-1b over two years was similar between treatments (23 vs 25, respectively; P value not reported). Both treatments were similar in regards to their effect on ARR (P=0.68).</p>
<p>Mikol et al.⁶⁹ (2008) REGARD GA 20 mg SC daily vs IFNβ-1a (Rebif®) 44 µg SC three times weekly</p>	<p>MC, OL, PG, RCT Patients between 18 and 60 years of age, naïve to both study drugs, diagnosed with RRMS with the McDonald criteria, an EDSS score 0 to 5.5, ≥1 attack within past 12 months and clinically stable or neurologically improving during the four weeks before study onset</p>	<p>N=764 96 weeks</p>	<p>Primary: Time to first relapse (defined as new or worsening neurological symptoms, without fever, lasting at least 48 hours and accompanied by a change in KFS score)</p> <p>Secondary: Proportion of patients relapse-free over study period, relapse rate, number of active T2 lesions (defined as new or enlarging per patient per scan over 96 weeks), mean number of gadolinium-</p>	<p>Primary: There was no significant difference in the time to first relapse between the IFNβ-1a and GA groups (HR, 0.94; 95% CI, 0.74 to 1.21; P=0.64).</p> <p>Secondary: There was no significant difference between treatment groups in the proportion of patients who were free from relapse over study period (P=0.96). There was no statistically significant difference between treatment groups in the ARR over the study period (P=0.828).</p> <p>There were no differences between treatment groups in the number of active T2 lesions (new or enlarging) per patient per scan over 96 weeks of therapy (P=0.18). No significant difference was reported between treatment groups in the mean change in T2 lesion volume over 96 weeks of therapy (P=0.26).</p> <p>Patients randomized to IFNβ-1a experienced a significantly lower number of gadolinium-enhancing lesions per patient per scan compared to the GA-treated group (0.24 vs 0.41; P=0.0002). Over the 96 weeks of therapy, a significantly greater number of patients randomized to IFNβ-1a were free of gadolinium-enhancing lesions compared to the GA-treated groups (81 vs 67%; P=0.0005).</p> <p>There were no significant difference between the groups in the mean</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<p>enhancing lesions/patient/scan, change in the volume of gadolinium-enhancing lesions, change in T2 volume, combined unique active lesions, new T1 hypointensities, T1 hypointense lesion volume, brain volume, disability progression, adverse effects</p>	<p>change in gadolinium-enhancing lesion volume over 96 weeks of therapy (P=0.42). Patients randomized to IFNβ-1a experienced a significantly lower number of combined unique active lesions per patient per scan compared to the GA-treated group (0.91 vs 1.22; P=0.01).</p> <p>There were no significant differences between treatment groups in the number of new T1 hypointense lesions per patient per scan over 96 weeks of therapy (P=0.15). No differences were reported between treatment groups in the mean change in new T1 hypointense lesion volume over 96 weeks of therapy (P=0.29).</p> <p>There was a significant reduction in brain volume among patients randomized to IFNβ-1a compared to the GA-treated group (P=0.018).</p> <p>There was no significant difference between the IFNβ-1a and GA groups in the proportion of patients with a six-month confirmed EDSS progression (11.7 vs 8.7%; P=0.117).</p> <p>Patients randomized to IFNβ-1a and GA experienced 632 and 618 treatment-related adverse effects, respectively (P value not reported). Treatment-related adverse events occurring significantly more often in the IFNβ-1a group than in the GA group included influenza-like illness, headache, myalgia and increased ALT (P<0.05). Treatment-related adverse events occurring significantly more often in the GA group than in the IFNβ-1a group included pruritus, swelling, induration at the injection site, dyspnea and post-injection systemic reactions (P<0.05).</p>
<p>Flechter et al.⁷⁰ (2002)</p> <p>GA 20 mg SC daily</p> <p>vs</p> <p>GA 20 mg SC every other day</p> <p>vs</p>	<p>OL, PRO</p> <p>Patients 18 years of age and older with clinically definite MS and ≥2 exacerbations within the previous two years</p>	<p>N=58</p> <p>2 years</p>	<p>Primary:</p> <p>Relapse rate, change in EDSS score and adverse effects</p> <p>Secondary:</p> <p>Not reported</p>	<p>Primary:</p> <p>At one and two years of follow-up, the relapse rate decreased significantly in all three treatment groups compared to baseline (P<0.05).</p> <p>While there were no significant changes in the EDSS scores from baseline at two years in the IFNβ-1b group (P=0.30), patients receiving GA daily or every other day experienced significantly higher (worsening) EDSS scores from baseline (P=0.007, P=0.04, respectively).</p> <p>There was no statistically significant difference in adverse events among the three treatment groups (P=NS).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p>				<p>IFNβ-1b groups reported the following adverse effects: flu-like symptoms, increased spasticity, injection-site reactions and systemic reactions.</p> <p>The treatment group receiving GA daily experienced the following adverse effects: flu-like symptoms, injection-site reactions, systemic reaction, lymphadenopathy and lipodystrophy. Side effects were generally reported within the first six months of therapy and resolved with continued therapy.</p> <p>Secondary: Not reported</p>
<p>Khan et al.⁷¹ (2001)</p> <p>GA 20 mg SC daily</p> <p>vs</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 µg IM once-weekly</p> <p>vs</p> <p>no treatment</p>	<p>MC, OL, PRO</p> <p>Patients with RRMS, ≥1 relapses in past two years and EDSS score ≤4</p>	<p>N=156</p> <p>12 months</p>	<p>Primary: Relapse rate</p> <p>Secondary: Changes in EDSS scores, relapse rate during each half of study, proportion of relapse-free patients and proportion of relapse-free patients during each half of the study</p>	<p>Primary: Relapse rates were 0.97, 0.85, 0.61 and 0.62 for patients receiving no treatment, IFNβ-1a, IFNβ-1b and GA, respectively. Reductions in the relapse rate compared to no treatment was only significant with IFNβ-1b (P<0.002) and GA (P<0.003) groups.</p> <p>Secondary: Mean EDSS scores were significantly reduced with IFNβ-1b (P<0.01) and GA (P<0.001) compared to no treatment.</p> <p>There were no significant reductions in relapse rates in the first half of the study and only GA-treated patients displayed a significant reduction in the second half (P=0.004).</p> <p>The proportions of relapse-free patients were 15, 20, 39 and 38% in the no treatment, IFNβ-1a, IFNβ-1b and GA groups, respectively. The differences between the IFNβ-1b and GA groups were statistically significant compared to the placebo group (P=0.037 and P=0.038, respectively). There was no significant difference between IFNβ-1a and placebo (P=NS).</p> <p>Of the 156 patients, 33 patients elected no treatment, 40 patients elected IFNβ-1a, 41 patients elected IFNβ-1b and 42 patients elected GA.</p>
<p>Khan et al.⁷²</p>	<p>MC, OL, PRO</p>	<p>N=156</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2001)</p> <p>GA 20 mg SC daily</p> <p>vs</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p> <p>vs</p> <p>no treatment</p>	<p>18 months follow up study in patients with RRMS and ≥1 relapse in the past two years and an EDSS score ≤4</p>	<p>18 months</p>	<p>Relapse rate</p> <p>Secondary: Change in EDSS scores, proportion of relapse-free patients</p>	<p>Relapse rates were 1.02, 0.81, 0.55 and 0.49 in the no treatment, IFNβ-1a, IFNβ-1b and GA groups, respectively. Reduction in the relapse rate compared to receiving no treatment was statistically significant only in the IFNβ-1b and GA (P=0.001 for both comparisons) groups.</p> <p>Secondary: Mean EDSS scores were significantly reduced only in the IFNβ-1b (P<0.01) and GA (P=0.003) groups compared to the no treatment group.</p> <p>The proportions of relapse-free patients were 6.7, 11.8, 32.4 and 33.3% in the no treatment, IFNβ-1a, IFNβ-1b and GA groups, respectively. A significantly greater proportion of patients in the IFNβ-1b and GA groups were relapse-free over 18 months of follow-up compared to patients receiving no treatment group (P=0.05). There was no significant difference in the proportion of relapse-free patients between IFNβ-1a and patients receiving no treatment (P>0.999).</p>
<p>O'Connor et al.⁷³ (2009)</p> <p>BEYOND</p> <p>GA 20 mg SC daily</p> <p>vs</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1b (Betaseron®) 0.50 mg SC every other day</p>	<p>DB, MC, PG, PRO, RCT</p> <p>Patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year</p>	<p>N=2,244</p> <p>24 months</p>	<p>Primary: Relapse risk</p> <p>Secondary: Progression on EDSS scale and change in T1-hypointense lesion volume</p>	<p>Primary: There were no differences in ARR between IFNβ-1b 0.25 and 0.50 mg (0.36 vs 0.33, respectively; P=0.10). In addition, no significant reductions in ARR were reported between GA and either dose of IFNβ-1b (0.34 vs 0.36 and 0.33 for the GA and the 0.25 and 0.50 mg doses of IFNβ-1b, respectively; P=0.42 and P=0.79).</p> <p>Secondary: The rate of progression on the EDSS scale was not significantly different between the IFNβ-1b groups and the GA group (21 to 27% across groups; P=0.55 to 0.71).</p> <p>Similarly, there were no differences in T1 hypointense lesion volume among treatment groups after two years compared to baseline values (P=0.18 to 0.68).</p>
<p>Carra et al.⁷⁴</p>	<p>MC, OS, PRO</p>	<p>N=114</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2008)</p> <p>GA 20 mg SC weekly for three years, subsequently switched to IFNβ or mitoxantrone therapy for additional three years</p> <p>vs</p> <p>IFNβ-1b (Betaseron[®]) 0.25 mg SC every other day for three years, subsequently switched to GA or mitoxantrone therapy for additional three years</p> <p>vs</p> <p>IFNβ-1a (Rebif[®]) 22 μg SC three times weekly for three years, subsequently switched to GA, IFNβ-1a 44 μg SC, IFNβ-1b, or mitoxantrone therapy for additional three years</p> <p>vs</p>	<p>Patients 18 years of age or older with RRMS, an EDSS disability score <6 and \geq1 relapse in the previous year</p>	<p>3-year, before switch period; 3-year, after switch period</p>	<p>ARR over the three-year post-switch treatment period</p> <p>Secondary: The proportion of patients relapse-free during the three-year post-switch treatment period and mean change in EDSS score over six years</p>	<p>The ARR was reduced by 77% (from 0.63 to 0.14) among patients who switched from IFNβ to GA therapy (P value not reported).</p> <p>The ARR was reduced by 71% (from 0.53 to 0.15) among patients who switched from IFNβ to mitoxantrone therapy (P value not reported).</p> <p>The ARR was reduced by 67% (from 0.52 to 0.17) among patients who switched from IFNβ to GA therapy (P value not reported).</p> <p>The smallest reduction (57%, from 0.37 to 0.16) in the ARR was observed in patients switched between different IFNβ preparations (P value not reported).</p> <p>The ARR was reduced by 75% (from 0.8 to 0.2) in the reference group over six years of therapy (P value not reported).</p> <p>Secondary: The proportion of relapse-free patients increased from 55 to 68% after switching from one IFNβ preparation to another (P value not reported).</p> <p>The proportion of relapse-free patients increased from 16 to 68% after switching from IFNβ to GA therapy due to inadequate efficacy (P value not reported). The proportion of relapse-free patients increased from 71 to 80% after switching from IFNβ to GA therapy due to adverse events (P value not reported).</p> <p>The proportion of relapse-free patients increased from 33 to 81% after switching from IFNβ to mitoxantrone therapy (P value not reported).</p> <p>The proportion of relapse-free patients increased from 27 to 63% after switching from GA to IFNβ therapy due to inadequate efficacy (P value not reported). The proportion of relapse-free patients decreased from 75 to 50% after switching from GA to IFNβ therapy due to adverse events (P value not reported).</p> <p>There was no evidence of disability progression as evidenced by a lack of statistically significant change in EDSS scores among patients</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>IFNβ-1a (Rebif®) 44 μg SC three times weekly for three years, subsequently switched to IFNβ-1b, GA or mitoxantrone therapy for additional three years</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly for three years, subsequently switched to IFNβ-1b, IFNβ-1a 44 μg SC, GA or mitoxantrone therapy for additional three years</p> <p>vs</p> <p>IFNβ or GA therapy for six years (reference cohort)</p>				<p>switching from IFNβ to GA due to inadequate efficacy or those switching from IFNβ to mitoxantrone (P>0.05). However, patients switching from one IFNβ to another or GA to IFNβ demonstrated a statistically significant disability progression (P<0.05).</p> <p>The change in EDSS scores was significantly higher among patients switching from GA to IFNβ compared to those switching from IFNβ to GA therapy (P=0.0035), suggesting a higher rate of disability progression in the latter group.</p> <p>There was no statistically significant change from baseline in EDSS score in the reference group six months after therapy initiation (P value not reported).</p>
<p>Haas et al.⁷⁵ (2005)</p> <p>GA 20 mg SC weekly</p> <p>vs</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p>	<p>OL, RETRO</p> <p>Patients with RRMS who have had one to three exacerbations within previous year and an EDSS score ≤3.5</p>	<p>N=308</p> <p>24 months</p>	<p>Primary: Relapse rate</p> <p>Secondary: Number of relapse-free patients, mean EDSS change and progression rate</p>	<p>Primary: The relapse rates decreased significantly for all drugs (P<0.05), with an ARR of 0.80, 0.69, 0.66 and 0.36 for IFNβ-1a 30 μg IM, IFNβ-1b, IFNβ-1a 22 μg SC and GA, respectively. There were no significant differences between the groups at six months, but the decline in relapse rate at 24 months was highest with GA (0.81; P<0.001).</p> <p>Secondary: The percentage of relapse-free patients at 24 months was 35.4, 45.5, 45.8 and 58.2% for IFNβ-1a 30 μg IM, IFNβ-1b, IFNβ-1a 22 μg SC and GA,</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>IFNβ-1a (Rebif®) 22 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p>				<p>respectively (P=NS). There were no significant differences in EDSS between groups (P=NS). The progression index declined in all treatment groups (P values were not reported).</p> <p>The discontinuation rate between six and 24 months was highest for IFNβ-1a 30 μg IM and lowest for GA (33 vs 9%; P<0.001).</p>
<p>Lublin et al.⁷⁶ (2013)</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly + GA 20 mg SC daily</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly + placebo SC daily</p> <p>vs</p> <p>GA 20 mg SC daily + placebo IM once-weekly</p>	<p>DB, MC, PC, Phase III, RCT</p> <p>Patients between the ages of 18 and 60 years with EDSS score of 0 to 5.5 and diagnosis of RRMS by Poser or McDonald criteria, with at least 2 exacerbations in the prior 3 years with no prior history of seizure activity</p>	<p>N=1,008</p> <p>36 months</p>	<p>Primary: Reduction in ARR as measured by protocol-defined exacerbations</p> <p>Secondary: Time to confirmed disability, MSFC score, MRI metrics, safety</p>	<p>Primary: ARR of IFNβ-1a + GA combination treatment group was similar to the ARR of GA + placebo treatment group (P=0.27). GA + placebo treatment group was significantly better than IFNβ-1a + placebo treatment group, reducing the risk of exacerbation by 31% (P=0.027) and the IFNβ-1a + GA combination treatment group was significantly better than IFNβ-1a + placebo treatment group, reducing the risk of exacerbation by 25% (P=0.022).</p> <p>There was no difference between the three treatment groups in time to first exacerbation (P=0.19). There was no difference between the groups in proportion of patients with relapses (IFNβ-1a + placebo vs GA + placebo, P=0.14; IFNβ-1a + GA vs IFNβ-1a + placebo, P=0.19; IFNβ-1a + GA vs GA + placebo, P=0.21).</p> <p>Secondary: There was no difference between the three treatment groups showing 6-month confirmed progression of EDSS with 23.9%, 21.6%, and 24.8% of patients with EDSS progression in the IFNβ-1a + GA, IFNβ-1a + placebo, and GA + placebo treatment groups, respectively.</p> <p>There was no difference between the three treatment groups in the MSFC score over 36 months with all groups showing small increases.</p> <p>Change in a composite score constructed from 4 MRI measures, Z4, from</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>baseline to month 36 did not differ between the IFNβ-1a + placebo and GA + placebo groups (P=0.52) or IFNβ-1a + GA and IFNβ-1a + placebo groups (P=0.23). Similarly, there were no differences between the groups at months 6, 12 and 24. The treatment groups were all effective in reducing MRI-defined disease activity measured by enhanced lesion numbers within 6 months of their initiation.</p> <p>The IFNβ-1a + GA combination treatment group reduced enhancement numbers more than IFNβ-1a + placebo group (P=0.01) when adjusted for baseline age and number of enhancements. There was no difference in the change in the number of enhancements from months 0 to 36 between IFNβ-1a + placebo and GA + placebo groups (P=0.82).</p> <p>The combination therapy with IFNβ-1a + GA did not result in any additional safety issues with the exception of the usual adverse events that were seen with the single agents. There were three deaths in the core study one in the extension study.</p>
<p>Koch-Henriksen et al.⁷⁷ (2006)</p> <p>IFNβ-1b (Betaseron[®]) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1a (Rebif[®]) 22 μg SC once-weekly</p>	<p>MC, OL, RCT</p> <p>Patients with RMSS who have had ≥ 2 relapses within two years and an EDSS score ≤ 5.5</p>	<p>N=421</p> <p>24 months</p>	<p>Primary: ARR, time to first relapse and NAb formation</p> <p>Secondary: Time to sustained progression</p>	<p>Primary: The ARR, time to first relapse and NAb formation were similar between patients taking either IFNβ therapy (P=NS).</p> <p>Secondary: There was no difference in the time to sustained progression between treatment arms (P=NS).</p> <p>Other: Side effects (15%) were the most frequent cause of withdrawal in the IFNβ-1b group and treatment failure was the most frequent cause of withdrawal in the IFNβ-1a group.</p>
<p>Baum et al.⁷⁸ (2007)</p> <p>BRIGHT</p> <p>IFNβ-1b (Betaseron[®]) 0.25 mg SC every other day</p>	<p>I, MC, OS, PRO</p> <p>Patients, mean age 36 years with RRMS and treated with either one of the study regimens</p>	<p>N=445</p> <p>15 consecutive injections (follow-up period, four to five</p>	<p>Primary: The proportion of patients pain-free during all injections (immediately, 30 minutes and 60 minutes post-injection)</p>	<p>Primary: A significantly greater proportion of patients receiving IFNβ-1b compared to IFNβ-1a were free from pain immediately, 30 minutes and 60 minutes after injection (P<0.0001 at all time points).</p> <p>Secondary: The proportion of pain-free injections per patient was significantly greater with IFNβ-1b compared to IFNβ-1a immediately, 30 minutes and</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>IFNβ-1a (Rebif®) 44 μg SC three times weekly</p>		<p>weeks)</p>	<p>Secondary: Proportion of injections that were pain free per patient, the mean visual analog scale per patient, impact of injection site pain on comfort and satisfaction with treatment</p>	<p>60 minutes after injection (P<0.0001 at all time points).</p> <p>Mean visual analog scale scores per patient were significantly lower with IFNβ-1b compared to IFNβ-1a immediately, 30 minutes and 60 minutes after injection (P<0.0001 at all time points).</p> <p>Injection site reactions occurred in significantly fewer patients treated with IFNβ-1b compared to IFNβ-1a (P<0.05).</p> <p>A significantly greater proportion of patients treated with IFNβ-1a compared to IFNβ-1b reported that pain after injection negatively impacted their satisfaction with treatment (35.9 vs 23.1%; P=0.006).</p> <p>Adverse effects were reported by 33.3% of patients treated with IFNβ-1b compared to 32.4% of patients receiving IFNβ-1a therapy (P value not reported).</p>
<p>Barbero et al.⁷⁹ (2006) INCOMIN</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p>	<p>MC, PG, PRO, RCT</p> <p>IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and EDSS scores 1 to 3.5</p>	<p>N=188</p> <p>2 years</p>	<p>Primary: Proportion of patients with ≥1 active MRI lesion</p> <p>Secondary: Total area/volume of brain lesions or burden of disease, correlation between primary outcome and NAb status</p>	<p>Primary: Significantly fewer patients had ≥1 active lesion in the IFNβ-1b arm compared to the IFNβ-1a arm (17 vs 34%; P<0.014).</p> <p>Secondary: The mean T2 burden of disease showed a progressive decrease from baseline in patients treated with IFNβ-1b and a progressive increase in patients treated with IFNβ-1a (P<0.001).</p> <p>The development of NABs did not appear to have any impact on changes in MRI activity associated with IFNβ-1b treatment during the entire study period (P=NS).</p>
<p>Durelli et al.⁸⁰ (2002) INCOMIN</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p>	<p>MC, PG, PRO, RCT</p> <p>IFNβ-naïve patients with RRMS and ≥2 exacerbations in prior two years and</p>	<p>N=188</p> <p>2 years</p>	<p>Primary: Proportion of patients free from relapses</p> <p>Secondary: ARR, annualized treated relapse rate,</p>	<p>Primary: Fifty-one percent of patients taking IFNβ-1b remained relapse-free compared to 36% of patients taking IFNβ-1a who remained relapse-free (P=0.03).</p> <p>Secondary: IFNβ-1b treatment resulted in fewer relapses per patient (0.5 vs 0.7; P=0.03), fewer treated relapses (0.38 vs 0.50; P=0.09), lower EDSS</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>IFNβ-1a (Avonex®) 30 µg IM once-weekly</p>	<p>EDSS scores 1 to 3.5</p>		<p>proportion of patients free from sustained and confirmed progression in disability, EDSS score and time to sustained and confirmed progression in disability</p>	<p>scores (2.1 vs 2.5; P=0.004), lower proportion of patients with progression in EDSS score of one point sustained for six months and confirmed at end of study (13 vs 30%; P=0.005) and longer time to sustained and confirmed disability progression (P<0.01) than IFNβ-1a treatment.</p> <p>Most adverse events (flu-like syndrome, fever, fatigue and increased liver enzymes) declined following six months of treatment. The frequency of adverse events was similar between groups. Local skin reactions and NABs were more common in patients treated with IFNβ-1b compared to patients treated with IFNβ-1a (P values not reported).</p> <p>NAB were reduced during the second year of treatment and did not appear to have any correlation with relapse rate.</p>
<p>Minagara et al.⁸¹ (2008) Murray⁸² (2004) PROOF</p> <p>IFNβ-1a (Rebif®) 44 µg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 µg IM once-weekly</p>	<p>DB, MC, OS, PRO, RETRO</p> <p>Patients between 18 and 50 years of age with RRMS and an EDSS score 0 to 5.5, at least two documented relapses during the three years before study onset, receiving IFNβ-1a 30 µg IM once-weekly or IFNβ-1a 44 µg SC three times weekly for at least 12 months and up to 24 months before enrollment</p>	<p>N=136</p> <p>12 to 24 months (RETRO phase)</p> <p>6 month (PRO phase)</p>	<p>Primary: Change in brain parenchymal fraction</p> <p>Secondary: Proportion of patients who experienced relapses at six months, ARR, change in EDSS, NAb formation and adverse effects</p>	<p>Primary: There was no significant difference between the groups in the change in brain parenchymal fraction (P value not reported).</p> <p>Secondary: There was no significant difference between the treatment groups in the rate of relapse (P value not reported).</p> <p>There was no significant difference between the groups in the change in EDSS scores, suggesting similar sustained disability progression in both the IM IFNβ-1a and IFNβ-1a 44 µg SC groups (25.8 vs 26.7%; P value not reported).</p> <p>More patients in the IFNβ-1a 44 µg SC group developed NABs compared to patients in the IM IFNβ-1a group (19 vs 0%; P value not reported).</p> <p>More patients positive for NABs compared to those negative for NABs had disability progression (40.0 vs 27.8%; P>0.05), new or enlarging T2 lesions (63.6 vs 40.7%; P=0.003) and gadolinium-enhancing lesions after 12 to 24 months of therapy (36.4 vs 15.0%; P=0.001).</p> <p>While general tolerability was comparable between the study drugs, IFNβ-1a 44 µg SC was associated with a greater incidence of injection-</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				site reactions compared to the IM formulation (6.0 vs 2.9%; P value not reported).
<p>Panitch et al.⁸³ (2002) EVIDENCE</p> <p>IFNβ-1a (Rebif®) 44 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p>	<p>MC, PG, RCT</p> <p>IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and EDSS score 0 to 5.5</p>	<p>N=677</p> <p>48 weeks</p>	<p>Primary: Proportion of patients who were relapse-free at 24 weeks</p> <p>Secondary: Relapse rate, time to first relapse and number of active lesions per patient per scan on MRI</p>	<p>Primary: More patients in the IFNβ-1a 44 μg SC treatment group compared to the IFNβ-1a 30 μg IM group remained relapse free at 24 (75 vs 63%; P=0.0005) and 48 weeks (62 vs 52%; P=0.009).</p> <p>Secondary: The time to first relapse was significantly prolonged in the IFNβ-1a 44 μg SC group compared to the IFNβ-1a 30 μg IM group (P=0.003).</p> <p>Patients receiving IFNβ-1a 44 μg SC compared to IFNβ-1a 30 μg IM had significantly fewer active MRI lesions (P<0.001).</p> <p>Injection-site reactions, asymptomatic abnormalities of liver enzymes, and altered leukocyte counts were more frequent with IFNβ-1a 44 μg SC compared to IFNβ-1a 30 μg IM (83 vs 28%; P<0.001, 18 vs 9%; P<0.002 and 11 vs 5%; P<0.003), respectively. NAbs developed in 25% of the IFNβ-1a 44 μg SC group compared to 2% of the IFNβ-1a 30 μg IM group (P<0.001).</p>
<p>Panitch et al.⁸⁴ (2005) EVIDENCE</p> <p>IFNβ-1a (Rebif®) 44 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p>	<p>MC, PG, RCT</p> <p>A 64-week follow-up of the EVIDENCE trial; IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and an EDSS score 0 to 5.5</p>	<p>N=677</p> <p>64 weeks</p>	<p>Primary: Proportion of patients who were relapse-free at 24 weeks</p> <p>Secondary: Relapse rate, time to first and second relapse, number of T2 active lesions per patient per scan, percentage of active scans per patient and proportion of patients with no active lesions</p>	<p>Primary: At study endpoint, 56% of patients in the IFNβ-1a 44 μg SC group and 48% of patients in the IFNβ-1a 30 μg IM group remained relapse-free (P=0.023).</p> <p>Secondary: In the IFNβ-1a 44 μg SC group compared to the IFNβ-1a 30 μg IM group, there was a 17% reduction in relapse rate, a delayed time to first relapse (HR, 0.70), and a 32% reduction in steroid use to treat relapses (P value not reported).</p> <p>Patients in the IFNβ-1a 44 μg SC group had decreased MRI activity with reductions in T2 active lesions and a lower proportion of active scans and increases in patients with no active scans compared to patients in the IFNβ-1a 30 μg IM treatment group (P<0.001, for all comparisons).</p> <p>The presence of NAbs was associated with reduced efficacy for MRI</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				measures and fewer IFN β -related adverse effects, but did not have a significant impact on relapse measures.
<p>Schwid et al.⁸⁵ (2005) EVIDENCE</p> <p>IFNβ-1a (Rebif[®]) 44 μg SC three times weekly vs IFNβ-1a (Avonex[®]) 30 μg IM once-weekly increased to 44 μg SC three times weekly</p> <p>Patients initially randomized to 30 μg IM once-weekly were allowed to switch to 44 μg SC three times a week after 48 weeks of therapy while patients initially randomized to 44 μg SC three times a week could withdraw from the study or continue on the regimen for an additional eight months.</p>	<p>ES, MC, PG, RCT</p> <p>An eight-month extension of the EVIDENCE trial; IFNβ-naïve patients with RRMS, ≥ 2 exacerbations in prior two years and an EDSS score 0 to 5.5</p>	<p>N=677</p> <p>80 weeks</p>	<p>Primary: Change in relapse rate</p> <p>Secondary: Change in the number of T2 active lesions per patient per scan, proportion of T2 active scans per patient and proportion of patients without T2 active scans</p>	<p>Primary: The relapse rate decreased from 0.64 to 0.32 for patients changing therapy (P<0.001) and from 0.46 to 0.34 for patients continuing therapy (P=0.03). The reduction in relapse rate was greater among patients switching to a higher dose and frequency IFNβ regimen (P=0.047).</p> <p>Secondary: Patients converting to the higher dose and frequency IFNβ regimen had fewer active lesions on T2-weighted MRI (P=0.02), fewer active scans (P=0.01) and no significant changes in the proportion of patients without active scans (P=NS). There were no significant changes in the continuing therapy group (P=NS).</p> <p>Seventy-three percent of the 306 patients receiving IFNβ-1a 30 μg IM switched to the IFNβ-1a 44 μg SC treatment and 91% of patients continued IFNβ-1a 44 μg SC therapy. Patients converting to the increased dose and frequency regimen experienced a higher incidence of adverse effects.</p>
<p>Schwid et al.⁸⁶ (2007) EVIDENCE</p>	<p>AB, I, MC, PG, RCT, XO</p>	<p>N=677</p> <p>80 weeks</p>	<p>Primary: Proportion of patients free of</p>	<p>Primary: A significantly greater proportion of patients randomized to receive IFNβ-1a 44 μg SC remained free from relapses during the comparative</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>IFNβ-1a (Rebif®) 44 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly, increased to 44 μg SC three times weekly</p> <p>Patients initially randomized to 30 μg IM once-weekly were allowed to switch to 44 μg SC three times a week after 48 weeks of therapy while patients initially randomized to 44 μg SC three times a week could withdraw from the study or continue on the regimen for an additional eight months.</p>	<p>Full results of the EVIDENCE trial; IFNβ-naïve patients, between 18 and 55 years of age, with RRMS, ≥2 exacerbations in prior two years and an EDSS score 0 to 5.5</p>		<p>relapses</p> <p>Secondary: Time to first relapse, ARR, number of steroid courses, number of T2 active lesions per patient per scan, percentage of active scans per patient, proportion of patients with no active scans, adverse events and NAbs detected</p>	<p>phase of the study, compared to patients receiving IFNβ-1a 30 μg IM once-weekly (56 vs 48%; OR, 1.5; 95% CI, 1.1 to 2.0; P=0.023).</p> <p>Secondary: Compared to patients in the IFNβ-1a 30 μg IM group, patients in the high-dose IFNβ-1a 44 μg SC group experienced a 30% reduction in the time to first relapse (HR, 0.70; P=0.002) during the comparative phase of the study.</p> <p>Compared to patients in the IFNβ-1a 30 μg IM group, patients in the high-dose, IFNβ-1a 44 μg SC group experienced a 17% reduction in ARR (P=0.033) during the comparative phase of the study.</p> <p>A 50% reduction in the mean ARR occurred among patients who switched from IFNβ-1a 30 μg IM to IFNβ-1a 44 μg SC (P<0.001) during the XO phase of the study.</p> <p>A 26% reduction in the mean ARR occurred among patients who continued to receive IFNβ-1a 44 μg SC (P=0.028) during the XO phase of the study.</p> <p>A significantly lower number of steroid courses per patient per year were used in the high-dose IFNβ-1a 44 μg SC group compared to the IFNβ-1a 30 μg IM group (0.19 vs 0.28; P=0.009) during the comparative phase of the study.</p> <p>Patients in the IFNβ-1a 44 μg SC group had a significantly fewer mean number of T2-active lesions compared to patients in the IFNβ-1a 30 μg IM group (0.9 vs 1.4; P<0.001) during the comparative phase of the study.</p> <p>A significant reduction in the mean number of T2-active lesions occurred among patients who converted from IFNβ-1a 30 μg IM to IFNβ-1a 44 μg SC during the XO phase of the study (P=0.022).</p> <p>Patients in the IFNβ-1a 44 μg SC group had a significantly lower percentage of T2-active scans per patient compared to patients in the</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>IFNβ-1a 30 μg IM group (27 vs 44%; P<0.001) during the comparative phase of the study.</p> <p>Patients who converted from IFNβ-1a 30 μg IM to IFNβ-1a 44 μg SC experienced a statistically significant reduction in the percentage of T2-active scans per patient during the XO phase of the study (P<0.001).</p> <p>A significantly greater percentage of patients randomized to the IFNβ-1a 44 μg SC group did not have a T2-active scan compared to patients in the IFNβ-1a 30 μg IM group (58 vs 38%; OR, 2.4; 95% CI, 1.7 to 3.3; P<0.001) during the comparative phase of the study.</p> <p>Converting from IFNβ-1a 30 μg IM to IFNβ-1a 44 μg SC was not correlated with a significant change in the percentage of patients with no T2-active scans (P=0.803).</p> <p>Patients who continued IFNβ-1a 44 μg SC therapy from the start of the study did not have significant changes in any of the MRI measures (P value not reported).</p> <p>Injection-site reactions were significantly more common in patients receiving IFNβ-1a 44 μg SC compared to patients receiving IFNβ-1a 30 μg IM (85 vs 33%; P<0.001). Flu-like symptoms were significantly more common in patients receiving IFNβ-1a 30 μg IM than in patients receiving IFNβ-1a 44 μg SC (53 vs 45%; P=0.031). Abnormal liver function test results were significantly more common in patients receiving IFNβ-1a 44 μg SC than in patients receiving IFNβ-1a 30 μg IM (18 vs 10%; P=0.003). Most liver enzyme elevations resolved with continued therapy.</p> <p>Abnormal WBC counts were significantly more common in patients receiving IFNβ-1a 44 μg SC compared to patients receiving IFNβ-1a 30 μg IM (14 vs 5%; P<0.001). WBC counts normalized in most patients with continued therapy.</p> <p>The development of NABs occurred in a significantly greater percentage of patients receiving IFNβ-1a 44 μg SC compared to patients receiving</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Traboulee et al.⁸⁷ (2008) EVIDENCE</p> <p>IFNβ-1a (Rebif®) 44 μg SC three times weekly vs IFNβ-1a (Avonex®) 30 μg IM once-weekly, increased to 44 μg SC three times weekly</p>	<p>PH</p> <p>This was a PH analysis of the EVIDENCE study; patients were included if had received at least one dose of the study drug and had an evaluable T2-weighted MRI scan obtained at baseline and week-48</p>	<p>N=533 48 weeks</p>	<p>Primary: Percentage change in T2 burden of disease from baseline to week-48</p> <p>Secondary: Absolute change in burden of disease, percentage and absolute change in burden of disease when stratified by NAb status from baseline to week-48</p>	<p>IFNβ-1a 30 μg IM (26 vs 3%; P<0.001). However, relapse rate was not affected by the NAb status (P=0.203).</p> <p>Primary: Median percentage decreases in burden of disease were greater in the IFNβ-1a 44 μg SC group compared to the IFNβ-1a 30 μg IM group (-6.7 vs -0.6%; P value not reported). The adjusted mean treatment difference in percentage change in burden of disease from baseline to week-48 showed a significant treatment benefit for patients treated with IFNβ-1a 44 μg SC compared to patients treated with IFNβ-1a 30 μg IM (-4.6%; SE, 2.6%; P=0.002).</p> <p>Secondary: A greater median absolute reduction from baseline in BOD was observed in the IFNβ-1a 44 μg SC group compared to IFNβ-1a 30 μg IM (-189.5 vs -19.0; P value not reported).</p> <p>Among patients randomized to IFNβ-1a 44 μg SC, median percentage decreases in burden of disease were smaller in patients positive for NAb compared to those with a negative NAb status (-0.8 vs -8.0; P value not reported).</p> <p>Among patients randomized to IFNβ-1a 44 μg SC, absolute decreases in burden of disease were smaller in patients positive for NAb compared to those with a negative NAb status (-46.2 vs -254.6; P value not reported).</p> <p>The adjusted mean treatment difference in percentage change in burden of disease from baseline to week-48 showed a significant treatment benefit for NAb negative patients treated with IFNβ-1a 44 μg SC compared to IFNβ-1a 30 μg IM treated patients (-6.6%; SE, 2.8%; P<0.0001).</p> <p>The adjusted mean treatment difference in percentage change in burden of disease from baseline to week-48 showed comparable treatment benefit for NAb positive patients treated with IFNβ-1a 44 μg SC compared to IFNβ-1a 30 μg IM treated patients (-0.5%; SE, 3.9%; P=0.583).</p>
<p>Etemadifar et al.⁸⁸</p>	<p>MC, RCT, SB</p>	<p>N=90</p>	<p>Primary:</p>	<p>Primary:</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(2006)</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1a (Rebif®) 44 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p>	<p>Patients with RRMS with ≥2 relapses in past two years and EDSS score ≤5</p>	<p>24 months</p>	<p>Number of relapses, proportion of relapse-free patients and EDSS scores</p> <p>Secondary: Not reported</p>	<p>Mean relapse rates were reduced from 2.0 to 1.2, 2.4 to 0.6 and 2.2 to 0.7 episodes (P<0.001 for each) for the IFNβ-1a 30 μg IM, IFNβ-1a 44 μg SC, and IFNβ-1b groups, respectively.</p> <p>The proportions of relapse-free patients were 20, 43 and 57% for IFNβ-1a 30 μg IM, IFNβ-1a 44 μg SC, and IFNβ-1b, respectively. The mean number of relapses were lower with IFNβ-1a 44 μg SC and IFNβ-1b compared to IFNβ-1a 30 μg IM treatment (P<0.05).</p> <p>EDSS scores decreased by 0.3 in the IFNβ-1a 44 μg SC group (P<0.05) and 0.7 in the IFNβ-1b group (P<0.001) while the IFNβ-1a 30 μg IM group remained stable.</p> <p>Secondary: Not reported</p>
<p>Rio et al.⁸⁹ (2005)</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1a (Rebif®) 22 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p>	<p>OL, OS, PM</p> <p>Patients with RRMS with ≥2 relapses in the previous two years and an EDSS score 0 to 5.5</p>	<p>N=495</p> <p>Up to 8 years</p>	<p>Primary: Proportion of relapse-free patients, proportion of patients with confirmed and sustained disability progression, ARR, proportion of decrease in relapse rate, proportion of patients reaching EDSS of six and number of patients who discontinued treatment due to inefficacy</p> <p>Secondary:</p>	<p>Primary: At two years 59, 59 and 50% of patients were relapse-free in the IFNβ-1a 30 μg IM, IFNβ-1a 22 μg SC, and IFNβ-1b groups, respectively. At four years 52, 39 and 35% of patients were relapse-free in the IFNβ-1a 30 μg IM, IFNβ-1a 22 μg SC and IFNβ-1b groups, respectively. Each group showed a significant reduction in relapse rate (P<0.0001). The number of relapses decreased with treatment at two years from 2.24 to 0.80 for IFNβ-1a 30 μg IM, from 2.51 to 0.64 for IFNβ-1a 22 μg SC and from 2.86 to 0.87 for IFNβ-1b. The relapse rates decreased at four years (from 1.07 to 0.33 for IFNβ-1a 30 μg IM, 1.21 to 0.41 for IFNβ-1a 22 μg SC, and from 1.36 to 0.38 for IFNβ-1b; P<0.0001 for all comparisons).</p> <p>The proportions of patients with confirmed and sustained disability at two and four years respectively, were 17 and 23% for IFNβ-1a 30 μg IM, 19 and 35% for IFNβ-1a 22 μg SC, and 10 and 24% for IFNβ-1b. There were no significant differences between the treatment groups (P=NS). Thirteen percent of patients had an EDSS ≥6 following four years of therapy, but there were no significant differences between groups (P=NS).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	<p>The proportions of patients discontinuing treatment due to lack of efficacy were 8% for IFNβ-1a 30 μg IM, 3% for IFNβ-1a 22 μg SC and 10% for IFNβ-1b (P values not reported).</p> <p>Patients selecting therapy with IFNβ-1a 30 μg IM were older than those selecting IFNβ-1a 22 μg SC. Patients selecting IFNβ-1b had greater disease activity and disability at baseline compared to the other treatments.</p> <p>Secondary: Not reported</p>
<p>Trojano et al.⁹⁰ (2003)</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1a (Rebif®) 22 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p>	<p>MC, OL, OS, PM</p> <p>Patients with RRMS</p>	<p>N=1,033</p> <p>24 months</p>	<p>Primary: Proportion of relapse-free patients and number of patients with ≥1 point progression in EDSS</p> <p>Secondary: Changes from baseline in ARR and EDSS score</p>	<p>Primary: The proportions of patients who were relapse free in each group were similar (54% with IFNβ-1a 30 μg IM, 49% with IFNβ-1a 22 μg SC and 54% with IFNβ-1b at 12 months (P value not reported). The proportions of patients who remained relapse free at 24 months were 33% with IFNβ-1a 30 μg IM and 38% with IFNβ-1b (P=NS).</p> <p>The number of patients experiencing ≥1 point progression in EDSS was 3% with IFNβ-1a 30 μg IM, 5% with IFNβ-1a 22 μg SC and 4% with IFNβ-1b at 12 months (P=NS). The number of patients with ≥1 point progression in EDSS at 24 months was 7% with IFNβ-1a 30 μg IM and 11% with IFNβ-1b (P=NS).</p> <p>Secondary: Relapse rates were 0.71 with IFNβ-1a 30 μg IM and 0.65 with IFNβ-1b (P=0.16). Mean changes in EDSS score were similar among the groups (P=NS).</p>
<p>Trojano et al.⁹¹ (2007)</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p>	<p>OS</p> <p>Patients with RRMS</p>	<p>N=1,504</p> <p>7 years</p>	<p>Primary: Incidence of SPMS</p> <p>Secondary: EDSS score of four and an EDSS score of six</p>	<p>Primary: Patients treated with IFNβ patients showed a reduction in the incidence of SPMS compared to untreated patients (P<0.0001) in terms of time from first visit (HR, 0.38) and current age (HR, 0.36).</p> <p>Secondary: There was a significant difference in favor of IFNβ-treated patients for</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>IFNβ-1a (Rebif®) 22 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Rebif®) 44 μg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p> <p>vs</p> <p>no treatment</p>				<p>EDSS score of four (P<0.02) and EDSS score of six (P≤0.03).</p>
<p>Limmroth et al.⁹² (2007) QUASIMS</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFNβ-1a (Rebif®) 22 μg SC three times weekly</p> <p>vs</p>	<p>MC, OS</p> <p>Patients 18 to 65 years of age with RRMS and uninterrupted ≥2 year history of therapy with one of the study regimens</p>	<p>N=4,754</p> <p>≥2 years</p>	<p>Primary:</p> <p>Change from baseline EDSS score, percentage of progression-free patients (defined as <1 point increase in EDSS score over two years of therapy), percentage of relapse-free patients, ARR and reasons for therapy change</p>	<p>Primary:</p> <p>There were no differences in the change from baseline EDSS scores among patients who received IFNβ-1a 30 μg IM, IFNβ-1b, IFNβ-1a 22 μg SC and IFNβ-1a 44 μg SC regimens over two years of therapy (0.17 vs 0.25 vs 0.20 vs 0.35, respectively; P value not reported).</p> <p>The percentage of progression-free patients was significantly lower in the IFNβ-1a 44 μg SC group compared to the IFNβ-1a 30 μg IM group (P<0.001) and IFNβ-1a 22 μg SC group (P=0.001).</p> <p>The percentage of progression-free patients was significantly lower in the IFNβ-1b group compared to the IFNβ-1a 30 μg IM group (P=0.001).</p> <p>The percentage of relapse-free patients was significantly lower in the IFNβ-1a 44 μg SC group compared to the IFNβ-1a 30 μg IM group (34.6 vs 48.5%; P=0.002) and IFNβ-1b group (34.6 vs 45.7%; P=0.007).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>IFNβ-1a (Rebif®) 44 µg SC three times weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 µg IM once-weekly</p>			<p>Secondary: Not reported</p>	<p>The percentage of relapse-free patients was significantly lower in the IFNβ-1a 22 µg SC group compared to the IFNβ-1a 30 µg IM group (39.8 vs 48.5%; P=0.005).</p> <p>There were no significant differences in ARR over two years among treatment-naïve patients who received IFNβ-1a 30 µg IM, IFNβ-1b, IFNβ-1a 22 µg SC and IFNβ-1a 44 µg SC regimens (0.51 vs 0.52 vs 0.53 vs 0.63, respectively; P=NS).</p> <p>The most common reason for therapy change was a perceived lack of efficacy (7.1%). A significantly greater percentage of patients changed therapy due to perceived lack of efficacy in the IFNβ-1a 22 µg SC group compared to either IFNβ-1a 30 µg IM (P=0.0027) or IFNβ-1b group (P<0.0001).</p> <p>Therapy change due to injection-site reactions was significantly less frequent among patients receiving IFNβ-1a 30 µg IM compared to IFNβ-1b (P<0.0001) and IFNβ-1a 22 µg SC groups (P=0.0001). In addition, a significantly greater percentage of patients in the IFNβ-1b group changed therapy due to flu-like symptoms compared to patients in the IFNβ-1a 22 µg SC group (1.2 vs 0.2 %; P=0.0038).</p> <p>Secondary: Not reported</p>
<p>Vermersch et al.⁹³ (2014) TENERE</p> <p>Teriflunomide 7 mg</p> <p>vs</p> <p>teriflunomide 14 mg</p> <p>vs</p> <p>Rebif® (IFNβ-1a) SC</p>	<p>DB, MC, PG, RCT</p> <p>Patients aged 18 years or older who met McDonald criteria for MS diagnosis and had relapsing clinical course, EDSS score of 5.5 or lower and no systemic corticosteroid use</p>	<p>N=324</p> <p>48 weeks</p>	<p>Primary: Time to failure</p> <p>Secondary: Safety and tolerability of teriflunomide, ARR, fatigue impact scale, global satisfaction score</p>	<p>Primary: Time to failure was not significantly different between groups (Rebif®: 42.3%; teriflunomide 7 mg: 48.6%, P=0.52; teriflunomide 14 mg: 37.8%, P=0.60).</p> <p>Secondary: The overall incidence of patients experiencing at least one TEAE was similar across all groups. The most common, potentially teriflunomide-related TEAEs were nasopharyngitis, diarrhea, alopecia, paresthesia and back pain and the most common potentially Rebif®-related TEAEs were headache, influenza-like illness and increased ALT.</p> <p>ARR was marginally lower in the Rebif® group (0.216) than the 7 mg</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>titrated to 8.8 µg for 2 weeks, 22 µg for 2 weeks then 44 µg; those who could not tolerate 44 µg were reduced to 22 µg</p>	<p>in 2 weeks prior to randomization</p>			<p>group (0.410; P=0.03) and was not significantly different from the 14 mg group (0.259; P=0.59).</p> <p>The increase from baseline in fatigue impact score was marginally lower in the Rebif® group (9.10) than the 7 mg group (0.97; P=0.03) and not statistically different than the 14 mg group (4.10; P=0.18).</p> <p>Patients in the Rebif® group expressed marginally lower global satisfaction scores (60.98) than patients in the 7 mg and 14 mg groups (68.29 and 68.82; P=0.02 for both).</p>
<p>Calabresi et al.⁹⁴ (2014) FREEDOMS II</p> <p>Fingolimod 0.5 mg QD</p> <p>vs</p> <p>fingolimod 1.25 mg QD</p> <p>vs</p> <p>placebo QD</p> <p>(all patients assigned to fingolimod 1.25 mg were switched to the 0.5 mg dose in a blinded manner after a review of data from other phase III trials and recommendation from the data and safety monitoring board, but were</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 55 years of age with RRMS who had one or more confirmed relapses during the preceding year (or two or more confirmed relapses during the previous two years), had EDSS score of 0 to 5.5, and had no relapse or steroid treatment within 30 days before randomization</p> <p>(previously treated patients were eligible if interferon β or glatiramer acetate therapy was</p>	<p>N=1,083</p> <p>24 months</p>	<p>Primary: Annualized relapse rate at month 24</p> <p>Secondary: Percentage brain volume change from baseline; time-to-disability-progression confirmed at three months</p>	<p>Primary: Patients given fingolimod had lower aggregate annualized relapse rates (over 24 months) than those given placebo (rate ratio, 0.5; 95% CI, 0.39 to 0.65; P<0.0001), corresponding to relative reductions in relapse rates compared to placebo of 50% in the 1.25 mg group and 48% in the 0.5 mg group (rate ratio, 0.52; 95% CI, 0.40 to 0.66; P<0.0001).</p> <p>Secondary: The mean percentage brain volume change from baseline was lower with both doses of fingolimod than it was with placebo at month 24 and the estimated treatment difference was statistically significant (1.25 mg dose, P<0.0001; 0.5 mg dose, P<0.0002. In general, patients given placebo had increased brain volume loss compared with those given fingolimod at months 6, 12, and 24.</p> <p>There was no statistically significant effect of fingolimod on time to disability progression confirmed at three months (1.25 mg dose, P=0.056; 0.5 mg dose, P=0.320) or six months (1.25 mg dose, P=0.113; 0.5 mg dose, P=0.101).</p> <p>The time to first confirmed relapse was delayed in both fingolimod treatment groups versus placebo (1.25 mg dose, HR, 0.50; 95% CI, 0.38 to 0.64; P<0.0001 and for the 0.5 mg dose, HR, 0.52; 95% CI, 0.40 to 0.67, P<0.0001), and more fingolimod-treated patients were relapse-free at the end of month 24. At month 24, patients given fingolimod had an improved median MSFC score compared with those given placebo.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
analyzed as being in the 1.25 mg group in the primary outcome analysis)	stopped at least three months before randomization and natalizumab treatment at least six months before randomization)			
<p>Confavreux et al.⁹⁵ (2014) TOWER</p> <p>Teriflunomide 7 mg QD</p> <p>vs</p> <p>teriflunomide 14 mg QD</p> <p>vs</p> <p>placebo QD</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 55 years of age with relapsing multiple sclerosis who had one or more relapse in the previous 12 months or two or more in the previous 24 months but no relapse in the previous 30 days and an EDSS score of 5.5 or less.</p>	<p>N=1,169</p> <p>48 weeks</p>	<p>Primary: Annualized relapse rate</p> <p>Secondary: Time to sustained accumulation of disability</p>	<p>Primary: The annualized relapse rate was higher in patients assigned to placebo (0.50, 95% CI, 0.43 to 0.58) than in those assigned to teriflunomide 14 mg (0.32, 95% CI, 0.27 to 0.38; P=0.0001) or teriflunomide 7 mg (0.39, 95% CI, 0.33 to 0.46; P=0.0183).</p> <p>Secondary: Compared with placebo, teriflunomide 14 mg reduced the risk of sustained accumulation of disability (HR, 0.68; 95% CI, 0.47 to 1.00, log-rank P=0.0442); however, teriflunomide 7 mg had no effect on sustained accumulation of disability (HR, 0.95; 95% CI, 0.68 to 1.35, log-rank P=0.7620).</p>
<p>Lublin et al.⁹⁶ (2013) ComiRX</p> <p>Interferon-β-1a (Avonex[®]) 30 μg IM weekly + glatiramer acetate (Copaxone[®]) 20 mg SQ QD</p> <p>vs</p> <p>interferon-β-1a</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 60 years of age with an EDSS score of 0 to 5.5 and diagnosed with RRMS with at least two exacerbations in the prior three years, where one exacerbation could be an MRI change</p>	<p>N=1,008</p> <p>3 years</p>	<p>Primary: Annualized relapse rate (only including protocol-defined relapses)</p> <p>Secondary: Confirmed progression of expanded disability status scale and change in a composite score</p>	<p>Primary: Annualized relapse rate of the combination group at 36 months was not significantly improved to the better of the 2 single-agent arms when adjusting for baseline age (P=0.27). Glatiramer acetate provided a significant reduction of risk of exacerbation compared to interferon by 31%, and the combination group provided a significant reduction of risk of exacerbation than interferon by 25% (P=0.027 and P=0.022 respectively). The results were similar combining protocol-defined exacerbation and with non-protocol defined exacerbations, a less stringent definition for exacerbation.</p> <p>Secondary: There were no differences between groups for the proportions showing</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>(Avonex[®]) 30 µg IM weekly + placebo SQ QD</p> <p>vs</p> <p>glatiramer acetate (Copaxone[®]) 20 mg SQ QD + placebo IM weekly</p>			<p>constructed from four MRI measures</p>	<p>six-month confirmed progression of EDSS, with progression observed in 22 to 25% of the participants. There was no difference in the m score between groups, with all groups showing small increases, primarily driven by the Paced Auditory Serial Addition Test. The 9-hole peg test and 25-foot timed walk were minimally worse after 36 months.</p> <p>The primary MRI outcome, change in the Z4 composite from baseline to month 36, did not differ between the interferon and glatiramer groups (P=0.52) or between the nominal monotherapy winner interferon and the combination (P=0.23), adjusted for baseline Z4 and age. Similarly, analyses at months six, 12, and 24 demonstrated no significant differences between the treatment arms.</p>
<p>Coles et al.⁹⁷ (2012)</p> <p>IFNβ-1a 44 µg SC three times weekly</p> <p>vs</p> <p>alemtuzumab 12 mg treatment regimen</p>	<p>AC, MC, RCT, rater-masked</p> <p>Patients 18 to 55 years of age with relapsing remitting MS with a maximum disease duration of 10 years, at least two attacks in the prior two years, at least one relapse while on interferon β or glatiramer after at least six months of treatment, EDSS scores of 5.0 or less, as well as cranial and spinal MRI lesions fulfilling protocol-defined criteria.</p>	<p>N=667</p> <p>2 years</p>	<p>Primary: Relapse rate and time to six month sustained accumulation of disability based on EDSS and MSFC</p> <p>Secondary: Change in T2-hyperintense lesion volume and safety endpoints</p>	<p>Primary: Alemtuzumab reduced the rate of relapse compared with IFNβ-1a (P<0.0001). Of the 426 patients treated with alemtuzumab, 147 patients experienced a relapse event (0.26 annualized relapse rate) compared with 102 of the 202 patients treated with IFNβ-1a (0.52 annualized relapse rate).</p> <p>Alemtuzumab reduced risk of sustained accumulation of disability compared with IFNβ-1a (P<0.0084). Of the 426 patients treated with alemtuzumab, 54 patients sustained confirmed disability accumulation (13% relapse rate) compared with 40 of the 202 patients treated with IFNβ-1a (20% relapse rate). Mean disability improved from baseline by -0.17 EDSS points after treatment with alemtuzumab (P=0.004) compared with a 0.24 EDSS point deterioration for IFNβ-1a (P=0.0064), resulting in a net benefit of treatment with alemtuzumab of 0.41 EDSS points (P<0.0001). MSFC scored improved from baseline by 0.08 after treatment with alemtuzumab and worsened on IFNβ-1a by -0.04, which was not noted to be a statistically significant difference (P=0.002).</p> <p>Secondary: There was no significant difference in the change in T2 lesion volume between the treatment groups. There was a -1.3% and -1.2% change in T2 lesion volume from baseline through year two for the alemtuzumab and IFNβ-1a treatment groups, respectively.</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>Cohen et al.⁹⁸ (2012)</p> <p>IFNβ-1a 44 µg SC three times weekly</p> <p>vs</p> <p>alemtuzumab 12 mg treatment regimen</p>	<p>AC, MC, RCT, rater-masked</p> <p>Patients 18 to 50 years of age with previously untreated relapsing remitting MS with a maximum disease duration of up to five years, at least two relapses in the previous two years, at least once relapse in the prior one year, EDSS scores of 3.0 or lower and cranial abnormalities on MRI attributable to MS</p>	<p>N=581</p> <p>2 years</p>	<p>Primary: Relapse rate and time to six month sustained accumulation of disability</p> <p>Secondary: Proportion of relapse-free patients, change in EDSS, percentage change in T2-hyperintense lesion volume, change in MSFC and safety endpoints</p>	<p>Of the 435 patients in the alemtuzumab treatment group, 393 patients (90%) had infusion-associated reactions, 334 patients (77%) had infections, 69 patients (16%) had thyroid disorders and three (1%) had immune thrombocytopenia. Of the 202 patients randomized to the IFNβ-1a group, 134 patients (66%) had infections.</p> <p>Primary: Alemtuzumab reduced the rate of relapse compared with IFNβ-1a (P<0.0001). Of the 376 patients treated with alemtuzumab, 82 patients experienced a relapse event (0.18 annualized relapse rate) compared with 75 of the 187 patients treated with IFNβ-1a (0.39 annualized relapse rate). A greater number of alemtuzumab-treated patients (77.6%), compared to IFNβ-1a-treated patients (58.7%), remained relapse free during the study (P<0.0001).</p> <p>Rates of sustained accumulation of disability did not differ between the treatment groups (P=0.22). Of the 376 patients treated with alemtuzumab, 30 patients sustained confirmed disability accumulation (8%) compared with 20 of the 202 patients treated with IFNβ-1a (11%).</p> <p>Secondary: Mean disability improved from baseline by 0.14 EDSS points in both the alemtuzumab and IFNβ-1a treatment groups (P=0.97).</p> <p>The difference in MSFC change between the treatment groups over 24 months was not statistically significant (P=0.01). There was a 0.15 mean change in MSFC score from baseline for the alemtuzumab treatment group and a 0.07 mean change in MSFC score from baseline for the IFNβ-1a treatment group.</p> <p>Decreases in T2-hyperintense lesions volume did not differ between the treatment groups over the 24 month time period (P=0.31). Compared with the IFNβ-1a treatment group (58% developed new or enlarging T2-hyperintense lesions), patients in the alemtuzumab treatment group (48% developed new or enlarging T2-hyperintense lesions) had a reduced proportion of new or enlarging T2-hyperintense lesions (P=0.04)</p> <p>Of the 376 patients in the alemtuzumab treatment group, 338 patients</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>(90%) had infusion-associated reactions and 12 patients (3%) had serious infusions reactions. Infections occurred in 67% of patients treated with alemtuzumab compared 45% of patients treated with IFNβ-1a. Thyroid-related disorders occurred in in 18% of patients treated with alemtuzumab compared 6% of patients treated with IFNβ-1a. Blood and lymphatic system disorders occurred in 18% of patients treated with alemtuzumab compared 19% of patients treated with IFNβ-1a. Two patients (1%) in the alemtuzumab treatment group developed thyroid papillary carcinoma. In the alemtuzumab treatment group, 98 serious adverse events occurred per year compared to 33 events per year in the IFNβ-1a treatment group.</p>
<p>Coles et al.⁹⁹ (2008)</p> <p>IFNβ-1a 44 µg SC three times weekly</p> <p>vs</p> <p>alemtuzumab 12 mg treatment regimen</p> <p>vs</p> <p>alemtuzumab 24 mg treatment regimen</p>	<p>AC, DB, MC, RCT</p> <p>Patients with previously untreated relapsing remitting MS with an onset of symptoms no more than 36 months before the time of screening, at least two clinical episodes during the previous two years, a score of 3 or less on the EDSS and once or more enhancing lesions as seen on cranial MRI scans</p>	<p>N=334</p> <p>36 months</p>	<p>Primary: Time to sustained accumulation of disability and the rate of relapse</p> <p>Secondary: Proportion of patients who did not have a relapse, changes in lesion burden, brain volume and safety endpoints</p>	<p>Primary: As compared with the IFNβ-1a treatment group, the alemtuzumab treatment groups reduced the risk of sustained disability by 71% (P<0.001): 75% risk reduction in the 12-mg group and 67% risk reduction in the 24-mg group. In both alemtuzumab treatment groups, the mean disability score on the EDSS improved by 0.39 point at 36 months: 0.32 points for the 12-mg dose (P=0.006) and 0.45 point for the 24-mg dose (P=0.001). The mean disability score worsened by 0.38 point among patients receiving IFNβ-1a, representing a net advantage of 0.77 points among patients receiving alemtuzumab (P<0.001).</p> <p>As compared with the IFNβ-1a treatment group, the alemtuzumab treatment groups had a reduced rated of relapse by 74% (P<0.001): 69% reduction in the 12-mg group and 79% reduction in the 24-mg group. The annualized relapse rate at 36 months was 0.36 for the IFNβ-1a group and 0.10 for the alemtuzumab treatment groups: 0.11 for the 12-mg group and the 0.08 for the 24-mg group.</p> <p>Secondary: The proportion of patients who remained relapse-free at 36 months was 52% for IFNβ-1a and 80% for the alemtuzumab treatment group: 77% for the 12-mg group and 84% for the 24-mg group (P<0.001).</p> <p>From baseline to month 36, there was a reduction in the volume of lesions, as seen on T2-weighted MRI, in all three study groups including a -13.3, -18.2 and -13.5 median change in lesion load on T2-weighted</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>MRI for the IFNβ-1a, alemtuzumab 12-mg and alemtuzumab 24-mg treatment groups, respectively (P=0.005).</p> <p>The reduction in brain volume between baseline and month 36 was significantly less among patients receiving alemtuzumab than among those receiving IFNβ-1a (-0.5% and -1.8, respectively; P=0.05).</p> <p>Of the 216 patients in the alemtuzumab treatment groups, 213 patients (98.6%) had infusion-associated reactions and 3 patients (1.4%) had serious infusions reactions. Infections occurred in 65.7% of patients treated with alemtuzumab compared 46.7% of patients treated with IFNβ-1a. Thyroid-related disorders occurred in 22.7% of patients treated with alemtuzumab compared 2.8% of patients treated with IFNβ-1a. Immune thrombocytopenic purpura occurred in 2.8% of patients treated with alemtuzumab compared 0.9% of patients treated with IFNβ-1a. Three patients (1.4%) in the alemtuzumab treatment group developed malignancies compared to one patient (0.9%) in the IFNβ-1a treatment group. Two patients (0.9%) in the alemtuzumab treatment group died compared to zero patients in the IFNβ-1a treatment group.</p>
<p>Calabresi et al.¹⁰⁰ (2014) ADVANCE</p> <p>Peginterferon β-1a 125 μg SC every two weeks</p> <p>vs</p> <p>Peginterferon β-1a 125 μg SC every four weeks</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 65 years of age with a diagnosis of RRMS, a score of zero to five on the EDSS, two clinically documented relapses in the previous three years, with one having occurred within 12 months prior to randomization</p>	<p>N=1,012</p> <p>48 weeks</p>	<p>Primary: Annualized relapse rate at week 48</p> <p>Secondary: Number of new or newly enlarging hyperintense lesions on T2-weighted images, proportion of patients who relapsed, and proportion of patients with disability progression at 48 weeks</p>	<p>Primary: Relapses were significantly less frequent in patients taking Peginterferon β-1a than in those taking placebo. At week 48, the adjusted annualized relapse rate was 0.397 relapses per patient-year (95% CI, 0.328 to 0.481) in the placebo group, 0.256 (95% CI, 0.206 to 0.318) in the every two weeks group, and 0.288 (95% CI, 0.234 to 0.355) in the every four weeks group. The rate ratio for peginterferon every two weeks compared to placebo was 0.644 (95% CI, 0.500 to 0.831; P=0.0007) and the rate ratio for peginterferon every four weeks compared to placebo was 0.725 (95% CI, 0.565 to 0.930; P=0.0114). Hazard ratios show significant reductions in risk of relapse after treatment with study drug relative to placebo. When placebo is compared to the every two weeks group the HR was 0.61 (95% CI, 0.47 to 0.80; P=0.0003) and when compared to the every four weeks group the HR was 0.74 (95% CI, 0.57 to 0.95; P=0.02).</p> <p>Secondary: The proportion of patients who had had 12 weeks of sustained disability progression at 48 weeks was 0.105 in the placebo group and 0.068 in</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<p>both intervention groups. Hazard ratios show that peginterferon β-1a significantly reduced the risk of progression of disability (HR, 0.62; 95% CI, 0.40 to 0.97; P=0.0383).</p> <p>Patients treated with peginterferon β-1a had fewer new or newly enlarging hyperintense lesions on T2-weighted images at 48 weeks than did patients in the placebo group; these lesions were also significantly smaller for those patients taking study drug compared to those taking placebo (P<0.0001).</p> <p>Patients in the every two weeks group had significantly fewer and smaller new T1 hypointense and gadolinium-enhancing lesions, and significantly fewer new active lesions, compared to patients in the placebo group (all P<0.0001). Patients in the every four weeks group had fewer new active lesions and smaller T2 and gadolinium-enhancing lesions compared to those in the placebo group (P<0.0001). There were fewer T1 hypointense and gadolinium-enhancing lesions, with peginterferon β-1a every four weeks compared to placebo, but differences were not statistically significant (P values not reported).</p> <p>There was no significant difference for whole brain volume between groups. Mean percentage decrease in magnetization transfer ratio was significantly lower for patients in the every two weeks group, compared to those in the placebo group (P=0.0438); however, there was no statistically significant difference when comparing those treated to peginterferon every four weeks with those treated with placebo (P=0.6873).</p> <p>The adverse events that were >2% more common in the peginterferon β-1a groups than in the placebo group were injection-site reactions, influenza-like illness, pyrexia, and headache. The most commonly reported treatment-related adverse events were injection-site reactions, influenza-like illness, and headache. The incidence of adverse events that led to discontinuation of study treatment was higher in the intervention groups than the placebo group (P values not reported). A greater proportion of patients in the intervention groups had reductions of hematological parameters and increased liver enzymes compared to</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients in the placebo group; however, most were not clinically significant and did not result in discontinuation of treatment. The incidence of serious adverse events was similar in each group.
Other				
<p>Comi et al.¹⁰¹ (2009) PRECISE GA 20 mg SC daily vs placebo</p>	<p>DB, DD, MC, PG, PRO, RCT Patients aged 18 to 45 years of age, with one unifocal neurological event in the previous 90 days, and positive brain MRI (defined as at least two cerebral lesions on the T2-weighted images at least 6 mm in diameter)</p>	<p>N=481 Up to 36 months</p>	<p>Primary: Time to conversion to clinically definite MS Secondary: Number of new T2 lesions detected at last scan, T2 lesion volume at last scan, percent change in brain volume (atrophy) and proportion of patients converting to clinically definite MS</p>	<p>Primary: There was a 45% reduction in the risk of conversion to clinically definite MS associated with GA compared to placebo (HR, 0.55; 95% CI, 0.40 to 0.77; P=0.0005). In addition, the time for 25% of patients to convert to clinically definite MS was significantly longer with GA compared to placebo (722 vs 336 days; P=0.0041). Secondary: The new number of new T2 lesions on MRI at the last visit was significantly reduced in patients treated with GA compared to patients randomized to placebo (0.7 vs 1.8; P<0.001). In PH analyses of patients completing two years of treatment without conversion to clinically definite MS, the cumulative number of new T2 lesions was reduced by 43% (RR, 0.57; 95% CI, 0.45 to 0.72; P<0.0001) of the MRI activity during the first year and by 52% (RR, 0.48; 95% CI, 0.3 to 0.61; P<0.0001) during the entire two years with GA compared to placebo. The reduction in the number of new T2 lesions corresponded with a reduction in lesion volume for patients treated with GA compared to patients randomized to placebo (geometric means ratio, 0.75; 95% CI, 0.64 to 0.87; P=0.0002). Fewer patients who were treated with GA experienced a second attack and converted to clinically definite MS compared to patients randomized to placebo (24.7 vs 42.9%; P<0.0001).</p>
<p>Clerico et al.¹⁰² (2008) IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p>	<p>MA DB, PC, RCTs of patients with clinically isolated syndrome treated</p>	<p>N=1,160 (3 studies) 2 to 3 years</p>	<p>Primary: The proportion of patients who converted to clinically definite MS</p>	<p>Primary: The proportion of patients converting to clinically definite MS was significantly lower in the IFNβ group compared to the placebo-treated group both at one year (OR, 0.53; 95% CI, 0.40 to 0.71; P<0.0001) and two years of follow-up (OR, 0.52; 95% CI, 0.38 to 0.70; P<0.0001).</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs</p> <p>IFNβ-1a (Rebif®) 22 μg SC weekly</p> <p>vs</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p> <p>vs</p> <p>placebo</p>	<p>with either IFNβ or GA therapy</p>		<p>Secondary:</p> <p>Side effects/adverse events</p>	<p>Secondary:</p> <p>Flu-like syndrome and injection site reactions occurred more frequently in patients receiving IFNβ compared to placebo: flu-like syndrome and injection-site reactions (P<0.00001). There was no significant difference in the incidence of serious adverse events between the two groups (P value not reported).</p>
<p>Bell et al.¹⁰³ (2007)</p> <p>GA 20 mg SC daily</p> <p>vs</p> <p>IFNβ-1b (Betaseron®) 0.25 mg SC every other day</p> <p>vs</p> <p>IFN-1a (Rebif®) 22 to 44 μg SC three times weekly</p> <p>vs</p> <p>AA</p> <p>IFNβ-1a (Avonex®) 30 μg IM once-weekly</p>	<p>CE</p> <p>Patients diagnosed with RRMS in the United States</p>	<p>N=3,151</p> <p>Up to 10 years</p>	<p>Primary:</p> <p>Incremental cost per QALY gained, cost per year spent in EDSS 0 to 5.5, cost per relapse-free year, cost per life-year gained</p> <p>Secondary:</p> <p>Not reported</p>	<p>Primary:</p> <p>The incremental cost per QALY gained was \$258,465, \$337,968, \$416,301, and \$310,691 for GA, IFNβ-1a 30 μg IM, IFNβ-1a 22 to 44 μg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management.</p> <p>The incremental cost per year spent in EDSS 0 to 5.5 was \$21,667, \$28,293, \$41,008, and \$27,860 for GA, IFNβ-1a 30 μg IM, IFNβ-1a 22 to 44 μg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management.</p> <p>The incremental cost per relapse-free year was \$17,599, \$24,327, \$32,207, and \$23,065 for GA, IFNβ-1a 30 μg IM, IFNβ-1a 22 to 44 μg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management.</p> <p>The incremental cost per life-year gained was \$2,076,622, \$2,588,087, \$3,378,626, and \$2,452,616 for GA, IFNβ-1a 30 μg IM, IFNβ-1a 22 to 44 μg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management.</p> <p>Consequently, compared to symptomatic management alone, GA was</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<p>vs symptomatic management</p>				<p>found to be the most CE immunomodulatory therapy option for MS. Secondary: Not reported</p>
<p>Prosser et al.¹⁰⁴ (2004) GA vs IFNβ-1b (Betaseron®) vs IFNβ-1a (Avonex®) vs no treatment Details of the clinical studies, including medication doses, used for the CE were not reported.</p>	<p>CE Hypothetical cohorts of patients with non-primary progressive MS</p>	<p>N=not reported 10 years</p>	<p>Primary: Gain in quality-adjusted life expectancy, incremental CE ratios in dollars per QALY gained Secondary: Not reported</p>	<p>Primary: Ten-year therapy with IFNβ-1a was associated with the largest gain in quality-adjusted life expectancy (QALY, 7.955) with an incremental CE ratio of \$2,200,000/QALY for women and \$1,800,000/QALY for men, compared to no treatment. For five-year treatment duration, no treatment strategy was associated with more quality-adjusted life years compared to alternative treatments. CE ratios were similar across all treatment groups. Secondary: Not reported</p>
<p>Noyes et al.¹⁰⁵ (2011) GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg</p>	<p>CE Patients diagnosed with RRMS and SPMS in the United States</p>	<p>N=1,121 10-year simulated disease progression cohort</p>	<p>Primary: Net gain in quality-adjusted life expectancy, incremental CE ratios in dollars per QALY gained Secondary:</p>	<p>Primary: The net gain in QALYs after 10 years of treatment with disease modifying therapy compared to supportive treatment was 0.192, 0.173, 0.082 and 0.126 years for IFNβ-1a 30 µg IM, IFNβ-1b 0.25 mg, IFNβ-1a 22 to 44 µg SC and GA, respectively. The CE of all disease modifying treatments exceeded \$900,000/QALY. IM IFNβ-1a 30 µg was associated with the lowest incremental cost per QALY at \$901,319. The incremental cost/QALY for IFNβ-1b 0.25 mg</p>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SC every other day vs IFN-1a (Rebif®) 22 to 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs symptomatic management			Not reported	and IFNβ-1a 22 to 44 µg SC were similar, costing \$1,123,162 and \$1,487,306, respectively. Treatment with GA was calculated to cost \$2,178,555 per QALY. Investigators reported that disease modifying therapies were associated with reduced costs/QALY and were more likely to become CE when drug costs were reduced and treatment was initiated earlier in the disease. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, GA=glatiramer acetate, IFNβ=interferon beta, IM=intramuscularly, IV=intravenous, QD=once daily, SC=subcutaneously, TID=three times daily
 Study abbreviations: AAR=absolute risk reduction, AB=assessor-blind, CE=cost-effectiveness study, CI=confidence interval, DB=double blind, DD=double dummy, ES=extension study, HR=hazard ratio, I=international, ITT=intention-to-treat, MA=meta-analysis, MC=multi-center, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PH=post-hoc analysis, PM=post-marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, RRR=relative risk reduction, SB=single-blind, SE=standard error, SR=systematic review, XO=crossover
 Miscellaneous abbreviations: ALT=alanine aminotransferase, ARR=annualized relapse rate, ATRS=Adductor Tone Rating Scale, EDSS=expanded disability status scale, GPS=global pain score, KFS=Kurtzke functional score, MAS=Modified Ashworth Scale, MRI=magnetic resonance imaging, MS=multiple Sclerosis, MSFC=multiple sclerosis functional composite, MSIS-29=multiple Sclerosis Impact Scale-29, NAb=neutralizing antibody, PBVC=percent brain volume change, PSFS=Penn Spasm Frequency Scale, QALY=quality-adjusted life years, RRMS=relapsing-remitting MS, SPMS=secondary progressive MS, TEAE=treatment emergent adverse event, WBC=white blood cell, WHO=world health organization, WMD=weighted mean difference

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 12. Relative Cost of the Immunomodulatory Agents used to treat Multiple Sclerosis

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Daclizumab	injection	Zinbryta [®]	\$\$\$\$\$	N/A
Dimethyl fumarate	capsule	Tecfidera [®]	\$\$\$\$\$	N/A
Fingolimod	capsule	Gilenya [®]	\$\$\$\$\$	N/A
Glatiramer acetate	injection	Copaxone ^{®*} , Glatopa ^{®†}	\$\$\$\$\$	\$\$\$\$\$
Interferon β-1a	injection	Avonex [®] , Avonex Pen [®] , Rebif [®] , Rebif Rebidose [®]	\$\$\$\$\$	N/A
Interferon β-1b	injection	Betaseron [®] , Extavia [®]	\$\$\$\$\$	N/A
Natalizumab	injection	Tysabri [®]	\$\$\$\$\$	N/A
Peginterferon β-1a	injection	Plegridy [®]	\$\$\$\$\$	N/A
Teriflunomide	tablet	Aubagio [®]	\$\$\$\$\$	N/A

N/A=Not available

*Generic available in at least one dosage form or strength.

†Glatopa[®] is a generic equivalent of Copaxone[®] 20 mg.

X. Conclusions

Several immunomodulatory agents are Food and Drug Administration (FDA)-approved for the treatment of adult patients with relapsing forms of multiple sclerosis (MS), including the injectable products daclizumab (Zinbryta[®]), glatiramer acetate (Copaxone[®], Glatopa[®]), natalizumab (Tysabri[®]), interferon β (IFNβ)-1b (Betaseron[®], Extavia[®]),

intramuscular (IM) IFN β -1a (Avonex[®]), subcutaneous (SC) IFN β -1a (Rebif[®]), SC peginterferon β -1a (Plegridy[®]) and the oral products dimethyl fumarate (Tecfidera[®]), fingolimod (Gilenya[®]), and teriflunomide (Aubagio[®]).¹⁻¹⁴ In April 2015, the FDA approved the first generic disease-modifying therapy for MS: Glatopa[®] 20 mg/mL. Glatopa[®] approval utilized the Abbreviated New Drug Application (ANDA) regulatory pathway, which is the pathway used for development and FDA approval of generic drugs. Glatopa[®] is fully substitutable for Copaxone[®] 20 mg/mL for relapsing-forms of MS.^{5,14,19} There are no other generic MS products available, including other strengths of glatiramer acetate.¹⁻¹⁴

Current clinical guidelines generally recommend the immunomodulatory agents as first line agents.^{17,18,26} All available agents have been shown to decrease MRI lesion activity, prevent relapses, delay disease progression, and ultimately reduce disability from MS.²⁸⁻¹⁰⁰ The goals of MS therapy include slowing disease progression, reducing relapse rate and preventing or postponing long-term disability. The Multiple Sclerosis Coalition recommends initiation of treatment with an FDA-approved disease-modifying therapy as soon as possible following a diagnosis of relapsing disease, noting that the factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed collaboratively by the individual and treating clinician.²⁶ Consensus guidelines from The American Academy of Neurology and the National MS Society (reaffirmed 2008) disease management guidelines recommend use of injectable disease modifying therapies, including , interferon beta (Avonex[®] [interferon beta-1a], Betaseron[®] [interferon β -1b], Extavia[®] [interferon β -1b] and Rebif[®] [interferon β -1a]) and Copaxone[®] (glatiramer acetate), for all patients with relapsing remitting MS.¹⁸ Recently revised guidance from the Association of British Neurologists for the prescribing of disease-modifying treatments in MS (2015) categorize therapies for relapsing remitting MS into two groups including agents of moderate efficacy (β interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod) and agents of high efficacy (alemtuzumab and natalizumab). Guidelines recommend starting with a moderate efficacy therapy, given their superior safety profile compared to the high efficacy therapies.¹⁷ Guidelines have not yet incorporated the use of daclizumab, which should not be used as a first line agent. Because of its safety profile, the use of daclizumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.¹

There are head-to-head trials comparing newer immunomodulatory agent to one of the interferons. The TRANSFORM trial compared fingolimod to IFN β -1a 30 mcg IM every week.³⁹ Fingolimod had significantly lower annualized relapse rate (ARR) (P<0.001), but there were no differences in disability progression. In the TENERE trial, the ARR for teriflunomide 7 mg was significantly higher than that of teriflunomide 14 mg and interferon β -1a 44 mcg three times a week.⁹³ Despite the higher relapse rates, patients rated teriflunomide better on the Treatment Satisfaction Questionnaire for Medication domains of Global Satisfaction, Convenience, and Side Effects. In the CONFIRM trial, there were no significant differences between dimethyl fumarate and glatiramer acetate for ARR, though both were more effective than placebo.⁶⁶ There were no significant differences between any of the groups in confirmed disability progression sustained for 12 weeks.

The most frequently reported adverse events associated with IFN β therapy are influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain. Rare cases of hepatic toxicity have occurred in patients who were treated with IFN therapy.¹³⁻¹⁴ Therapy with IFN β should be used cautiously in patients with depression or other mood disorders. Patients receiving glatiramer acetate therapy may experience a transient, self-limiting, post-injection systemic reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria) immediately following drug administration.^{4,5} Fingolimod has been associated with cardiac-related death and thus requires cardiac monitoring. It is contraindicated in patients with certain pre-existing cardiovascular conditions.³ Teriflunomide has boxed warnings regarding hepatotoxicity and its risk of teratogenicity.¹² Dimethyl fumarate appears to have the most mild side effect profile with its most common adverse events being flushing and gastrointestinal effects.² Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing treatment with natalizumab, physicians should consider whether the expected benefit is sufficient to offset this risk. Natalizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH[®] Prescribing Program because of the risk of PML.^{9,15,27} Because of the risks of hepatic injury, including autoimmune hepatitis, and other immune-mediated disorders, daclizumab is also available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZINBRYTA REMS Program.¹ Because of its safety profile, the use of daclizumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.¹

The drugs in this American Hospital Formulary Service (AHFS) class are used in a specific patient population. Because very specific criteria must be met prior to initiating therapy, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand immunomodulatory agent used to treat multiple sclerosis within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand immunomodulatory agent used to treat multiple sclerosis is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Zinbryta[®] [package insert]. North Chicago (IL): AbbVie Inc.; 2016 May.
2. Tecfidera[®] [package insert]. Cambridge (MA): Biogen Idec Inc.; 2017 Jan.
3. Gilenya[®] [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2016 Feb.
4. Copaxone[®] [package insert]. Kansas City (MO): Teva Neuroscience, Inc.; 2014 Jan.
5. Glatopa[®] [package insert]. Princeton (NJ): Sandoz, Inc.; 2016 Jan.
6. Betaseron[®] [package insert]. Whippany (NJ): Bayer Healthcare Pharmaceuticals. Inc.; 2016 Apr.
7. Extavia[®] [package insert]. East Hanover (NJ): Novartis Pharmaceuticals; 2016 May.
8. Rebif[®] [package insert]. Rockland (MA): EMD Serono, Inc; 2015 Nov.
9. Tysabri[®] [package insert]. Cambridge (MA): Biogen Idec Inc.; 2016 May
10. Plegridy[®] [package insert]. Cambridge (MA): Biogen Idec Inc.; 2016 Jul.
11. Avonex[®] [package insert]. Cambridge (MA): Biogen Idec, Inc.; 2015 Dec.
12. Aubagio[®] [package insert]. Cambridge (MA): Genzyme Corporation; 2016 Nov.
13. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Mar]. Available from: <http://www.thomsonhc.com/>.
14. Facts and Comparisons[®] eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Mar 2017]. Available from: <http://online.factsandcomparisons.com>.
15. Olek MJ. Disease-modifying treatment of relapsing-remitting multiple sclerosis in adults. In: Gonzalez-Scarano F (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2017 [cited 2017 Mar 6]. Available from: <http://www.uptodate.com/utd/index.do>.
16. Olek MJ. Treatment of progressive multiple sclerosis in adults. In: Gonzalez-Scarano F (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2017 [cited 2017 Mar 6]. Available from: <http://www.uptodate.com/utd/index.do>.
17. Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol*. 2015 Aug;15(4):273-9. doi: 10.1136/practneurol-2015-001139. Epub 2015 Jun 22.
18. Goodin DS, Frohman EM, Garmany GP. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58(2):169-78.
19. Momenta Pharmaceuticals Announces FDA Approval of ANDA for Glatopa(TM) (glatiramer acetate injection), the First Substitutable Generic for COPAXONE(R) (glatiramer acetate injection) 20mg [press release on the internet]. Cambridge (MA): Momenta Pharma; 2015 Apr 16 [cited 2017 Mar 9]. Available from: <http://ir.momentapharma.com/releasedetail.cfm?releaseid=907001>.
20. Kappos L. Interferons in multiple sclerosis. *Neurol Clin*. 2005;23:189-214.
21. National Institute for Health and Clinical Excellence (NICE). Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 55 p. (Technology appraisal guidance; no. 254).
22. National Institute for Health and Clinical Excellence (NICE). Teriflunomide for treating relapsing-remitting multiple sclerosis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2014 Jan. (Technology appraisal guidance; no. 303).
23. National Institute for Health and Clinical Excellence. Multiple Sclerosis in Adults: Management. London: NICE CG186; 2014 OCT. Available from: <https://www.nice.org.uk/guidance/cg186>.
24. Goodin DS, Frohman EM, Hurwitz B. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2007;68(13):977-84.
25. National Clinical Advisory Board of the National Multiple Sclerosis Society. Expert Opinion Paper: Disease Management Consensus Statement. National Multiple Sclerosis Society, 2008 [cited 2013 Oct 14]. Available from: <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/index.aspx>.
26. The Multiple Sclerosis Coalition. The Use of Disease-Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence. A Consensus Paper by the Multiple Sclerosis Coalition. July 2014. Available from: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color.
27. National Institute for Health and Care Excellence (NICE). Natalizumab for the treatment of adults with high active relapsing-remitting multiple sclerosis [guideline on the Internet]. 2007 [cited 2013 Oct 14].

28. Kappos L, Wiendl H, Selmaj K, Arnold DL, Havrdova E, Boyko A, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med*. 2015 Oct 8;373(15):1418-28. doi: 10.1056/NEJMoa1501481.
29. Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, Radue EW, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2013 Jun 22;381(9884):2167-75. doi: 10.1016/S0140-6736(12)62190-4. Epub 2013 Apr 4.
30. Giovannoni G, Gold R, Selmaj K, Havrdova E, Montalban X, Radue EW, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECTION): a multicentre, randomised, double-blind extension trial. *Lancet Neurol*. 2014 May;13(5):472-81. doi: 10.1016/S1474-4422(14)70039-0. Epub 2014 Mar 19.
31. Gold R, Radue EW, Giovannoni G, et al. Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study. *BMC Neurol*. 2016 Jul 26;16:117. doi: 10.1186/s12883-016-0635-y.
32. Giovannoni G, Radue EW, Havrdova E, Riester K, Greenberg S, Mehta L, et al. Effect of daclizumab high-yield process in patients with highly active relapsing-remitting multiple sclerosis. *J Neurol*. 2014 Feb;261(2):316-23. doi: 10.1007/s00415-013-7196-4. Epub 2013 Dec 29.
33. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012 Sep 20;367(12):1098-107.
34. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387-401.
35. Devonshire V, Havrdova E, Radue EW, O'Connor P, Zhang-Auberson L, Agoropoulou C, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomized, placebo-controlled FREEDOMS study. *Lancet Neurol*. 2012 May;11(5):420-8.
36. Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med*. 2006;355:1124-40.
37. Radue EW, O'Connor P, Polman CH, Hohlfeld R, Calabresi P, Selmaj K, et al. Impact of fingolimod therapy on magnetic resonance imaging outcomes in patients with multiple sclerosis. *Arch Neurol*. 2012 Oct;69(10):1259-69.
38. Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. *Mult Scler*. 2012 Sep;18(9):1269-77.
39. Cohen JA, Barkhof F, Comi G, Hartung P, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362:402-15.
40. Khatri B, Barkhof F, Comi G, Hartung HP, Kappos L, Montalban X, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomized extension of the TRANSFORMS study. *Lancet Neurol*. 2011 Jun;10(6):520-9.
41. Cohen JA, Khatri B, Barkhof F, et al. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. *J Neurol Neurosurg Psychiatry*. 2016 May;87(5):468-75.
42. Meca-Lallana JE, Balseiro JJ, Lacruz F, Guijarro C, Sanchez O, Cano A, et al. Spasticity improvement in patients with relapsing-remitting multiple sclerosis switching from interferon- β to glatiramer acetate: the Escala Study. *J Neurol Sci*. 2012 Apr 15;315(1-2):123-8.
43. Ford C, Goodman AD, Johnson K, Kachuck N, Lindsey JW, Lisak R, et al. Continuous long-term immunomodulatory therapy in relapsing multiple sclerosis: results from the 15-year analysis of the US prospective open-label study of glatiramer acetate. *Mult Scler*. 2010 Mar;16(3):342-50.
44. Boneschi FM, Rovaris M, Johnson KP. Effects of glatiramer acetate on relapse rate and accumulated disability in multiple sclerosis: meta-analysis of three double-blind, randomized, placebo-controlled clinical trials. *Multiple Sclerosis*. 2003;9:349-55.
45. Caon C, Din M, Ching W, Tselis A, Lisak R, Khan O. Clinical course after change of immunomodulating therapy in relapsing-remitting multiple sclerosis. *European Journal of Neurology*. 2006;13:471-4.
46. Zwiibel HL. Glatiramer acetate in treatment-naïve and prior interferonb-1b-treated multiple sclerosis patients. *Acta Neurol Scand*. 2006;113:378-86.
47. Miller A, Spada V, Beerkircher D, Kreitman RR. Long-term (up to 22 years), open-label, compassionate-use study of glatiramer acetate in relapsing-remitting multiple sclerosis. *Multiple Sclerosis*. 2008;14:494-9.
48. La Mantia L, Munari LM, Lovati R. Glatiramer acetate for multiple sclerosis. *Cochrane Database Syst Rev*. 2010 May 12;(5):CD004678.
49. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R; GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol*. 2013 Jun;73(6):705-13.

50. Carmona O, Casado V, Moral E. Interferon- β 1b in multiple sclerosis: effect on progression of disability and clinical markers of treatment response. *Eur Neurol.* 2008;60:279-84.
51. PRISMS Study Group. Randomized double-blind placebo-controlled study of interferon β -1a in relapsing/remitting multiple sclerosis. *Lancet.* 1998;352:1498-504.
52. Kappos L, Traboulsee A, Constantinescu C. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. *Neurology.* 2006;67:944-53.
53. Rice GP, Incurvaia B, Munari LM, Ebers G, Polman C, D'Amico R, et al. Interferon in relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev.* 2009 Jan 19;(1):CD002002.
54. Freedman MS, Hughes B, Mikol DD, Bennett R, Cuffel B, Divan V, et al. Efficacy of disease-modifying therapies in relapsing-remitting multiple sclerosis: a systematic comparison. *Eur Neurol.* 2008;60(1):1-11.
55. Coppola G, Lanzillo R, Florio C. Long-term clinical experience with weekly interferon beta-1a in relapsing multiple sclerosis. *Eur J Neurol.* 2006;13:1014-21.
56. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med.* 2006 Mar 2;354(9):899-910.
57. Lublin FD, Cutter G, Giovannoni G, Pace A, Campbell NR, Belachew S. Natalizumab reduces relapse clinical severity and improves relapse recovery in MS. *Mult Scler Relat Disord.* 2014 Nov;3(6):705-11.
58. Fox RJ, Cree BA, De Sèze J, et al. MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study. *Neurology.* 2014 Apr 29;82(17):1491-8.
59. Outteryck O, Ongagna JC, Brochet B, et al. A prospective observational post-marketing study of natalizumab-treated multiple sclerosis patients: clinical, radiological and biological features and adverse events. The BIONAT cohort. *Eur J Neurol.* 2014;21(1):40-8.
60. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med.* 2006 Mar 2;354(9):911-23.
61. Kalincik T, Horakova D, Spelman T, et al. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. *Ann Neurol.* 2015 Mar;77(3):425-35.
62. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med.* 2011 Oct;365:1293-303.
63. O'Connor P, Comi G, Freedman MS, et al. Long-term safety and efficacy of teriflunomide: Nine-year follow-up of the randomized TEMSO study. *Neurology.* 2016 Mar 8;86(10):920-30.
64. Freedman MS, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Teriflunomide added to interferon- β in relapsing multiple sclerosis: a randomized phase II trial. *Neurology.* 2012 Jun;78:1877-85.
65. Confavreux C, Li DK, Freedman MS, Truffinet P, Benzerdjeb H, et al. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. *Mult Scler.* 2012 Sep;18(9):1278-89.
66. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med.* 2012 Sep 20;367(12):1087-97.
67. Castelli-Haley J, Oleen-Burkey MKA, Lage MJ, Johnson KP. Glatiramer acetate vs interferon beta-1a for subcutaneous administration: comparison of outcomes among multiple sclerosis patients. *Adv Ther.* 2008;25(7):658-73.
68. Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K, et al. Efficacy of treatment of MS with IFN β -1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology.* 2009 Jun 9;72(23):1976-83.
69. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous acetate in patients with relapsing multiple sclerosis (the Rebif vs Glatiramer acetate in Relapsing MS Disease [REGARD] study): a multicenter, randomized, parallel, open-label trial. *Lancet Neurol.* Oct.2008;7:903-14.
70. Flechter S, Vardi J, Rabey JM. Comparison of glatiramer acetate (Copaxone[®]) and interferon β -1b (Betaseron[®]) in multiple sclerosis patients: an open-label 2-year follow-up. *J Neurol Sci.* 2002;197:51-5.
71. Khan OA, Tselis AC, Kamholz JA. A prospective, open-label treatment trial to compare the effect of IFN β -1b (Betaseron[®]), and glatiramer acetate (Copaxone[®]) on the relapse rate in relapsing-remitting multiple sclerosis. *Eur J Neurol.* 2001;8:141-8.
72. Khan OA, Tselis AC, Kamholz JA, Garbern JY, Lewis RA, Lisak RP. A prospective, open-label treatment trial to compare the effects of IFN β -1a (Avonex[®]), IFN β -1b (Betaseron[®]), and glatiramer acetate (Copaxone[®]) on the relapse rate in relapsing-remitting multiple sclerosis: results after 18 months of therapy. *Multiple Sclerosis.* 2001;7:349-53.
73. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 μ g or 500 μ g interferon beta-1b vs 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomized, multicentre study. *Lancet Neurol.* 2009 Oct;8(10):889-97.

74. Carra A, Onaha P, Luetic G. Therapeutic outcome three years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. *European Journal of Neurology*. 2008;15:386-93.
75. Haas J, Firzlaiff M. Twenty-four-month comparison of immunomodulatory treatments – a retrospective open label study in 308 RRMS patients treated with beta interferons or glatiramer acetate (Copaxone). *Eur J Neurol*. 2005;12:425-31.
76. Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol*. 2013 Mar;73(3):327-40.
77. Koch-Henriksen N, Sorensen PS, Christensen T. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. *Neurol*. 2006;66:1056-60.
78. Baum K, O'Leary C, Coret Ferrer F, Klímová E, Procházková L, Bugge J. Comparison of injection site pain and injection site reactions in relapsing-remitting multiple sclerosis patients treated with interferon beta-1a or 1b. *Mult Scler*. 2007 Nov;13(9):1153-60.
79. Barbero P, Bergui M, Versino E. Every-other-day interferon beta-1b vs once-weekly interferon beta-1a for multiple sclerosis (INCOMIN Trial) II: analysis of MRI responses to treatment and correlation with Nab. *Multiple Sclerosis*. 2006;12:72-6.
80. Durelli L, Verdun E, Barbero P. Every-other-day interferon beta-1b vs once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomized multicentre study (INCOMIN). *Lancet*. 2002;359:1453-60.
81. Minagara A, Murray TJ. Efficacy and tolerability of intramuscular interferon beta-1a compared to subcutaneous interferon beta-1a in relapsing MS: results from PROOF. *Curr Med Res Opin*. 2008; 24(4):1049-55.
82. Murray TJ. Rationale and design of the prospective and retrospective study of Avonex and Rebif (PROOF) for the treatment of relapsing-remitting multiple sclerosis. *Curr Med Res Opin*. 2004; 20(1):25-30.
83. Panitch H, Goodin D, Francis G. Randomized, comparative study of interferon beta-1a treatment regimens in MS: the EVIDENCE trial. *Neurol*. 2002;59:1496-506.
84. Panitch H, Goodin D, Francis G. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. *J Neurol Sci*. 2005;239:67-74.
85. Schwid SR, Thorpe J, Sharief M. Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing multiple sclerosis. The EVIDENCE study. *Arch Neurol*. 2005;62:785-92.
86. Schwid SR, Panitch HS. Full results of the evidence of interferon dose-response European North American comparative efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly vs high dose, high-frequency interferon β -1a for relapsing multiple sclerosis. *Clin Ther*. 2007;29(9):2031-48.
87. Traboulsee A, Sabbagh AL, Bennett R, Chang P, Li DKB. Reduction in magnetic resonance imaging T2 burden of disease in patients with relapsing-remitting sclerosis: analysis of 48-week data from the EVIDENCE (evidence of interferon dose-response: European North American comparative efficacy) study. *BMC Neurol*. 2008 Apr 21;8:11.
88. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaseron, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. *Acta Neurol Scand*. 2006;113:283-7.
89. Rio J, Tintore M, Nos C, et al. Interferon beta in relapsing-remitting multiple sclerosis: an eight years' experience in a specialist multiple sclerosis center. *J Neurol*. 2005;252:795-800.
90. Trojano M, Liguori M, Paolicelli D. Interferon beta in relapsing-remitting multiple sclerosis: an independent post marketing study in southern Italy. *Multiple Sclerosis*. 2003;9:451-7.
91. Trojano M, Pellegrini F, Fuiani A. New natural history of interferon-beta-treated relapsing multiple sclerosis. *Ann Neurol*. 2007;61:300-6.
92. Limmroth V, Malessa R, Zettl UK. Quality assessments in multiple sclerosis therapy (QUASIMS). *J Neurol*. 2007;254:67-77.
93. Vermersch P, Czlonkowska A, Grimaldi LM, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Mult Scler*. 2014 May;20(6):705-16.
94. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014 Jun;13(6):545-56. doi: 10.1016/S1474-4422(14)70049-3.

95. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2014 Mar;13(3):247-56. doi: 10.1016/S1474-4422(13)70308-9. Epub 2014 Jan 23.
96. Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol.* 2013 Mar;73(3):327-40. doi: 10.1002/ana.23863. Epub 2013 Mar 11.
97. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease modifying therapy: a randomized controlled phase 3 trial. *Lancet.* 2012 Nov 24; 380(9856):1829-39.
98. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomized controlled phase 3 trial. *Lancet.* 2012 Nov 24; 380(9856):1819-28.
99. Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab versus interferon beta-1a in early multiple sclerosis. *New England Journal of Medicine.* 2008 Oct 23; 359 (17):1786-801.
100. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon β -1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol.* 2014 Jul;13(7):657-65. doi: 10.1016/S1474-4422(14)70068-7. Epub 2014 Apr 30.
101. Comi G, Martinelli V, Rodegher M, Moiola L, Bajenaru O, Carra A, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISE study): a randomized, double-blind, placebo-controlled trial. *Lancet.* 2009 Oct 31;374(9700):1503-11.
102. Clerico M, Faggiano F, Palace J, Rice G, Tintorè M, Durelli L. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. *Cochrane Database Syst Rev.* 2008 Apr 16; (2):CD005278.
103. Bell C, Graham J, Earnshaw S, Oleen-Burkey M, Castelli-Haley J, Johnson K. Cost-effectiveness of four immunomodulatory therapies for relapsing-remitting multiple sclerosis: a Markov model based on long-term clinical data. *J Manag Care Pharm.* 2007 Apr;13(3):245-61.
104. Prosser LA, Kuntz KM, Bar-OR A, Weinstein MC. Cost-effectiveness of interferon beta-1a, interferon beta-1b, and glatiramer acetate in newly diagnosed non-primary progressive multiple sclerosis. *Value Health.* 2004 Sep-Oct;7(5):554-68.
105. Noyes K, Bajorska A, Chappel A, Schwid SR, Mehta LR. Cost-effectiveness of disease-modifying therapy for multiple sclerosis: a population-based study. *Neurology.* 2011 Jul 26;77(4):355-63.

**Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review of Dyanavel XR®
Amphetamines: AHFS Class 282004
May 10, 2017**

I. Overview

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common psychiatric disorder that is often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.¹⁻² The key diagnostic feature is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.¹ There are three subtypes of ADHD, including a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype in which both symptoms are displayed.¹ Untreated (or undertreated) ADHD is associated with adverse sequelae, including conduct disorder, antisocial personality traits, substance abuse, and other comorbidities.¹

There are several central nervous system agents that are approved for the treatment of ADHD. This includes cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine, extended-release clonidine, and extended-release guanfacine.³⁻⁵ The stimulants are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.³⁻⁵ Due to their potential for abuse, the stimulants are classified as Schedule II controlled substances.

Dyanavel® XR (amphetamine) is a central nervous system stimulant indicated for the treatment of ADHD in patients six years and older. Dyanavel® XR uses a patented delivery system consisting of both immediate- and extended-release amphetamine and is the only once-daily, extended-release, amphetamine-based oral liquid approved to treat ADHD in children.³⁻⁶

The amphetamine products included in this review are listed in Table 1. Dyanavel® XR (amphetamine) is not available in a generic formulation.

Table 1. Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amphetamine	extended-release suspension	Dyanavel® XR	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cerebral Stimulants/Agents Used for ADHD

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit Hyperactivity Disorder in Children and Adolescents (2011) ⁷	<p>Preschool-aged children (four to five years of age)</p> <ul style="list-style-type: none"> The primary care clinician should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first-line of treatment. Methylphenidate may be prescribed if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. <p>Elementary school-aged children (six to 11 years of age)</p> <ul style="list-style-type: none"> The primary care clinician should prescribe Food and Drug Administration (FDA)-approved medications for attention deficit-hyperactivity disorder (ADHD) and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, preferably both. The evidence is particularly strong for stimulant medications and sufficient but

Clinical Guideline	Recommendation(s)
	<p>less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order).</p> <p><u>Adolescents (12 to 18 years of age)</u></p> <ul style="list-style-type: none"> The primary care clinician should prescribe FDA-approved medications for ADHD with the assent of the adolescent and may prescribe behavior therapy as treatment for ADHD, preferably both. <p><u>General considerations</u></p> <ul style="list-style-type: none"> Stimulant medications are highly effective for most children in reduction of core symptoms of ADHD. Atomoxetine, extended-release guanfacine and extended-release clonidine reduce core symptoms; however, they have a smaller evidence base than stimulants. Extended-release guanfacine and extended-release clonidine have evidence to support their use as adjunctive therapy with stimulant medications. Before beginning medication treatment for adolescents with newly diagnosed ADHD, clinicians should assess these patients for symptoms of substance abuse. Clinicians should monitor symptoms and prescription-refill requests for signs of misuse or diversion of ADHD medications and consider prescribing medications with no abuse potential, such as atomoxetine, extended-release guanfacine, or extended-release clonidine (which are not stimulants) or stimulant medications with less abuse potential, such as lisdexamfetamine, dermal methylphenidate, or osmotic-release oral system methylphenidate). Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects.
<p>Institute for Clinical Systems Improvement: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents (2012)⁸</p>	<p><u>Medication trials</u></p> <ul style="list-style-type: none"> Prescribe FDA-approved treatments for ADHD in children, including psychostimulants and/or non-stimulants. The decision to use medications should be made in conjunction with parents following a thorough discussion of expected benefits and potential risks. Factors such as the child's age, severity of symptoms and presence of comorbidity should also be considered and may involve decision-making regarding choice of medication. Obtain cardiology consultation for patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that could place patients at an increased risk to the sympathomimetic effects of central nervous system stimulants and/or atomoxetine. Review the personal and family cardiovascular history, and complete a physical examination of each patient prior to starting stimulant therapy and/or atomoxetine. Medication history or physical exam changes consistent with possible cardiac disease during treatment with stimulant medication and/or atomoxetine may require additional evaluation by a cardiologist. Optimal medication management alone is superior to other modalities for the core symptoms of ADHD. Response to one stimulant does not predict response to the others. If a child is a non-responder to one stimulant, it is advisable to attempt a second or third trial with other stimulants. Treatment with psychostimulants is often safe and effective in managing many children with ADHD with mild to moderate tics. Nevertheless, frequency and severity of tics should be carefully monitored in these patients. No routine blood work is necessary before or during psychostimulant therapy. Current evidence does not support a higher risk of sudden cardiac death with

Clinical Guideline	Recommendation(s)
	<p>stimulant medication compared to the general population; however, certain conditions may place a patient at higher risk for such an outcome.</p> <ul style="list-style-type: none"> Atomoxetine is a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or physician. Atomoxetine is a non-controlled substance that may make it preferable in certain clinical situations. Extended-release guanfacine and extended-release clonidine are the first ADHD medications to achieve FDA approval as adjunctive therapy with stimulant medications. Extended-release guanfacine is the first ADHD medication to look for improvement of oppositional symptoms in addition to ADHD core symptoms. <p><u>Alternative medications</u></p> <ul style="list-style-type: none"> When adequate stimulant, atomoxetine or alpha adrenergic trials are unsuccessful due to either poor response or adverse effects, or if associated comorbidity is present, alternative medication trials should be considered. Second-line medications for ADHD therapy include tricyclic antidepressants (imipramine, desipramine), alpha adrenergic agonist (clonidine) a non- tricyclic antidepressant (bupropion), or immediate-release guanfacine.
<p>National Institute for Health and Clinical Excellence: Attention Deficit Hyperactivity Disorder: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Children, Young People, and Adults (2008)⁹</p>	<p><u>Treatment for children and adolescents with ADHD</u></p> <ul style="list-style-type: none"> Methylphenidate, atomoxetine and dexamphetamine are recommended as options for the management of ADHD in children and adolescents. The decision regarding which product to use should be based on the following: <ul style="list-style-type: none"> The presence of comorbid conditions. The different adverse effects of the drugs. Specific issues regarding compliance identified for the individual child or adolescent. The potential for drug diversion. The preferences of the child/adolescent and/or his or her parent or guardian. Healthcare professionals should consider the following treatment recommendations: <ul style="list-style-type: none"> Methylphenidate for patients with ADHD without significant comorbidities. Methylphenidate for patients with ADHD with comorbid conduct disorder. Methylphenidate or atomoxetine when tics, Tourette’s syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present. Atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate. Modified-release preparations should be considered for the following reasons: <ul style="list-style-type: none"> Convenience. Improving adherence. Reducing stigma (because the child or young person does not need to take medication at school). Reducing problems schools have in storing and administering controlled drugs. Their pharmacokinetic profiles. Immediate-release preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels. <p><u>Treatment of adults with ADHD</u></p> <ul style="list-style-type: none"> Drug treatment is the first-line treatment for adults with ADHD with either

Clinical Guideline	Recommendation(s)
	<p>moderate or severe levels of impairment.</p> <ul style="list-style-type: none"> • Methylphenidate is recommended as the first-line drug. • If methylphenidate is ineffective or unacceptable, atomoxetine or dexamphetamine can be tried. • Caution should be exercised when prescribing dexamphetamine to those likely to be at risk of stimulant misuse or diversion.
<p>British Association of Psychopharmacology: Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology (2014)¹⁰</p>	<p><u>Treatment recommendations for children and adolescents</u></p> <ul style="list-style-type: none"> • All children with severe ADHD (conceptualized as hyperkinetic disorder) should be offered pharmacological treatment. In addition, consider pharmacological treatment for children with moderate symptoms of ADHD who have not responded to psychological interventions. • The treatment of choice for children with severe ADHD or moderate ADHD non-responsive to psychological treatments is psychostimulant medication. • Atomoxetine can be used instead when there is a risk of misuse of psychostimulants by children or the adults supporting the child. • Appropriate child and family-based psychological interventions should be available to all children with ADHD. These interventions should be tailored to the child's needs and not depend on the local availability of services. • Teachers should be given evidence-based information about ADHD. • Patient and parental preferences should be taken into account when designing a psychological intervention for ADHD. • Every effort should be made to facilitate the transition from adolescence to adulthood. This should include education of parents, children, and professionals involved in the care of these children and the development of appropriate services and shared care protocols to enable this transition. • Systems and protocols need to be implemented to allow early re-access to services for young people who may have dropped out of treatment at an early age, but still have significant symptoms and impairment. <p><u>Treatment recommendations for adults</u></p> <ul style="list-style-type: none"> • Stimulant medications are the first-line drugs in adults with ADHD. • Although amphetamines, methylphenidate and atomoxetine are all effective in adults with ADHD, they cannot be considered equivalent because they have different mechanisms of actions and hazards. • Once methylphenidate, atomoxetine, and amphetamines have all been given a fair trial, third-line medications can be considered. These include bupropion, modafinil, tricyclic antidepressants, guanfacine and clonidine. • Co-administration of psychostimulant and other drugs (mainly atomoxetine) is an option for patients showing a limited or lack of clinical response. There is, however, limited evidence supporting either the efficacy or safety of combination therapy. • Psychological treatments are a complement to pharmacological treatment. • Different approaches have been used but the majority the evidence is for structured treatments employing a cognitive behavioral paradigm. • The use of different methods of delivery (group and individual therapy), different criteria for control groups and different outcome measures limit the generalization of results. <p><u>Abuse potential</u></p> <ul style="list-style-type: none"> • Abuse potential is related to drug action and formulation. Abuse is generally low among patients but it can occur with stimulants. Slow-release preparations of these agents or atomoxetine are preferred for patients with a history of substance abuse, or who are at risk for substance abuse.

III. Indications

The Food and Drug Administration (FDA)-approved indications for Dyanavel® XR are noted in Table 3.

Table 3. FDA-Approved Indications for Dyanavel® XR³

Indication	Dyanavel® XR
Treatment of Attention Deficit Hyperactivity Disorder	✓

IV. Pharmacokinetics

The pharmacokinetic parameters of Dyanavel® XR are listed in Table 4. Dyanavel® XR consists of d-amphetamine and l-amphetamine in a ratio of 3.2:1. A single 18.8- mg dose of Dyanavel XR in healthy adult patients demonstrated an elimination half-life of approximately 12 hours for d-amphetamine and 15 hours for l-amphetamine. The delivery system uses ion exchange polymeric chemistry to deliver a continuous release of amphetamine throughout the day.³⁻⁶

Table 4. Pharmacokinetic Parameters of Dyanavel® XR⁴

Generic Name(s)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amphetamine extended-release suspension	20	Hepatic	Renal (30 to 40 unchanged; 50 as metabolites)	7 to 34

V. Drug Interactions

Major drug interactions with amphetamine are listed in Table 5.

Table 5. Major Drug Interactions with Amphetamine³

Generic Name(s)	Interaction	Mechanism
Amphetamines	MAOIs	Toxicity of amphetamines may be increased by MAOIs. Headache, hyperpyrexia, elevated blood pressure and bradycardia may occur. Amphetamines can liberate large quantities of intraneuronal norepinephrine that have accumulated during treatment with MAOIs.
Amphetamines	CYP2D6 inhibitors	The concomitant use of amphetamines and CYP2D6 inhibitors may increase the exposure of amphetamines compared to the use of the drug alone and increase the risk of serotonin syndrome.
Amphetamines	Urinary alkalinizers	Interaction may lead to pH-dependent diminished urinary elimination of amphetamines and increases risk of amphetamine toxicity.
Amphetamines	Urinary acidifying agents	Interaction may lead to pH-dependent increased urinary elimination of amphetamines and lower blood levels and efficacy of amphetamines.
Amphetamines	Serotonergic drugs	The concomitant use of amphetamine and serotonergic drugs increases the risk of serotonin syndrome.
Amphetamines	Tricyclic antidepressants	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

VI. Adverse Drug Events

The most common adverse drug events reported with amphetamines are listed in Table 6. The boxed warning for Dyanavel® XR is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with Amphetamine⁵

Adverse Events	Amphetamine
Cardiovascular	
Blood pressure increased	✓
Cardiomyopathy	✓
Palpitations	2 to 4
Peripheral vascular disease	—
Raynaud's disease	—
Tachycardia	6
Central Nervous System	
Aggressive behavior	—
Agitation	8
Anxiety	8
Depression	—
Dizziness	2 to 7
Drowsiness	2 to 4
Dyskinesia	✓
Dysphoria	✓
Euphoria	✓
Fever	5
Headache	26
Insomnia	12 to 27
Irritability	—
Labile affect	2 to 9
Mania	—
Nervousness	6
Overstimulation	✓
Psychotic episodes	—
Restlessness	✓
Seizures	—
Somnolence	—
Speech disorder	2 to 4
Stroke	—
Tic exacerbation	✓
Tourette's exacerbation	✓
Tremor	✓
Twitching	2 to 4
Dermatological	
Diaphoresis	—
Hyperhidrosis	2 to 4
Photosensitivity	2 to 4
Rash	—
Stevens-Johnson syndrome	—
Toxic epidermal necrolysis	—
Urticaria	✓
Gastrointestinal	
Abdominal pain	11 to 14
Anorexia	22 to 36
Appetite decreased	—
Constipation	2 to 4
Dental disease	2 to 4
Diarrhea	6
Dry mouth	—
Dyspepsia	2
Nausea	5 to 8
Other gastrointestinal disturbances	—
Unpleasant taste	—
Vomiting	7
Weight loss	4 to 10
Xerostomia	35

Adverse Events	Amphetamine
Genitourinary	
Changes in libido	2 to 4
Impotence	2 to 4
Prolonged erections	✓
Urinary tract infection	5
Other	
Accidental injury	3
Allergic rhinitis	4
Anaphylaxis	
Angioedema	
Blurred vision	
Dysmenorrhea	2 to 4
Dyspnea	
Epistaxis	4
Growth suppression	
Hypersensitivity reactions	
Infection	2 to 4
Tolerance	
Weakness	2 to 6

✓ Percent not specified.

-Event not reported or incidence <1%.

Table 7. Boxed Warning for Dyanavel® XR³

WARNING
<p>WARNING: ABUSE AND DEPENDENCE</p> <ul style="list-style-type: none"> CNS stimulants, including Dyanavel® XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

VII. Dosing and Administration

The usual dosing regimens for Dyanavel® XR are listed in Table 8.

Table 8. Usual Dosing Regimens for Dyanavel® XR³

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Amphetamine	<p><u>Treatment of Attention Deficit Hyperactivity Disorder:</u> Extended-release suspension: The dose should be individualized according to the needs and responses of the patient; maximum, 20 mg/day</p>	<p><u>Treatment of Attention Deficit Hyperactivity Disorder:</u> In children 6 years of age and older, start with 2.5 mg or 5 mg once daily in the morning. The dose may be increased in increments of 2.5 mg to 10 mg per day every four to seven days up to a maximum dose of 20 mg per day.</p>	<p>Extended-release suspension: 2.5 mg/mL</p>

VIII. Effectiveness

The FDA-approval of Dyanavel XR® (amphetamine) was based on the results of a phase III randomized, placebo-controlled clinical trial in 108 children with ADHD aged six to 12 years. The first five weeks of the study were an open-label dose optimization period, with an initial dose of 2.5 mg or 5 mg daily, followed by a one-week, double-blind treatment period. The study met its primary endpoint of change in pre-dose Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-combined score, an ADHD functional assessment tool, at four hours post-dosing. Secondary efficacy endpoints evaluated duration of onset and duration of action based on change in SKAMP-combined scores at 1, 2, 4, 6, 8, 10, 12 and 13 hours post-dose. The change in SKAMP-combined scores demonstrated a statistically significant improvement at all time points compared to placebo. These results are presented in the package insert.³ No additional clinical studies for Dyanavel XR® were identified. Clinical trials evaluating other amphetamine formulations are included in Table 8.

Table 8. Comparative Clinical Trials with Amphetamines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
McCracken et al. ¹¹ (2003) AMP-IR (Adderall®) 10 mg daily vs AMP-XR (Adderall XR®) 10 to 30 mg daily vs placebo	DB, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (combined or hyperactive-impulsive subtype)	N=51 5 weeks	Primary: SKAMP scales Secondary: Examination of the time course of AMP-XR	Primary: AMP-IR and AMP-XR were judged to have similar efficacy, and both exceeded placebo on attention and deportment SKAMP scales (P<0.0001). Secondary: The AMP-XR group displayed continued efficacy (in SKAMP score improvements) at time points beyond that of the AMP-IR group (i.e., 12 hours post dose).
Pliszka et al. ¹² (2000) AMP-IR (Adderall®) 12.5 mg daily vs MPH-IR	DB, PC, PG, RCT Children in grades one through five diagnosed with ADHD	N=58 3 weeks	Primary: CGI-S (parent and teacher) Secondary: Not reported	Primary: More responders were reported with AMP-IR than MPH-IR or placebo on both CGI-S scores (P<0.05). Behavioral effects of AMP-IR appeared to persist longer than with MPH-IR. Fourteen (70%) patients in the AMP-IR group required only a single morning dose, and 17 (85%) patients in the MPH-IR group received two or more doses per day (P=0.003). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
25 mg daily vs placebo				Not reported
Pelham et al. ¹³ (1999) AMP-IR (Adderall®) 7.5 or 12.5 mg twice daily vs MPH-IR (Ritalin®) 10 or 17.5 mg twice daily vs placebo	DB, PC, RCT, XO Children five to 12 years of age diagnosed with ADHD	N=25 6 weeks	Primary: Time course and dose-dependent response information Secondary: Not reported	Primary: Both doses of AMP-IR were generally more efficacious in reducing negative behaviors and improving academic productivity than low-dose MPH-IR (10 mg BID) throughout the course of the entire day. The differences were more pronounced when the effects of MPH-IR were wearing off at midday and late afternoon/early evening (P<0.025). Conversely, AMP-IR 7.5 mg BID and MPH-IR 17.5 mg BID produced equivalent behavioral changes throughout the entire day. The doses of AMP-IR that were assessed produced greater improvement than did the assessed doses of MPH-IR, particularly the lower dose of MPH-IR (P<0.01). Both drugs produced low and comparable levels of clinically significant side effects. Secondary: Not reported
Faraone et al. ¹⁴ (2002) AMP-IR (Adderall®) vs MPH-IR	MA (4 trials) Patients diagnosed with ADHD	N=216 3 to 8 weeks	Primary: CGI-S (parent, teacher and investigator) Secondary: Not reported	Primary: Combined results showed slightly greater efficacy with AMP-IR vs MPH- IR in clinician and parent ratings (P<0.05). No statistically significant difference was found in CGI-S scores with teacher ratings (P≥0.26). Secondary: Not reported
Biederman et al. ¹⁵ (2002) AMP-XR	DB, MC, PC, RCT Children six to 12 years of age	N=584 3 weeks	Primary: CGI-S (teachers and parents)	Primary: Each AMP-XR treatment group had a statistically significant improvement in both CGI-S teacher and parent scales (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Adderall XR®) 10 to 30 mg daily vs placebo	diagnosed with ADHD (hyperactive-impulsive or combined subtypes)		Secondary: Variation in responses based on morning and afternoon assessments	Secondary: The CGI-S teacher scores calculated for the morning and afternoon assessments showed all doses of AMP-XR to be more effective than placebo (P<0.001) at each assessment. The CGI-S teacher scores in the AMP-XR group were statistically significantly improved at all time points compared to those in the placebo group (P<0.001).
Goodman et al. ¹⁶ (2005) AMP-XR (Adderall XR®) 10 to 60 mg daily	MC, OL, PRO Adults ≥18 years of age diagnosed with ADHD (any subtype)	N=725 10 weeks	Primary: ADHD-RS, CGI-I Secondary: SF-36	Primary: At the end of the study, the mean ADHD-RS scores significantly decreased in the AMP-XR group regardless of dose compared to baseline (P<0.0001). Statistical analysis comparing the individual AMP-XR doses was not performed. At the end of the study, most patients obtained CGI-I ratings of much/very much improved (522/702; 74.4%). Secondary: At the end of the study, the AMP-XR groups reported significant improvements in all quality of life measurements (P<0.0001 for all) measured by the SF-36, including physical functioning and mental health parameters.

Drug regimen abbreviations: AMP=mixed amphetamine salts, DEX=dextroamphetamine, DXM=dexmethylphenidate, ER=extended release, IR=immediate release, LDX=lisdexamfetamine, MPH=methylphenidate, OROS=osmotic-release oral system, SR=sustained release, XR=extended release
 Study abbreviations: CI=confidence interval, DB=double blind, DR=dosing ranging, ES=extension study, FD=fixed dose, HR=hazard ratio, MA=meta-analysis, MC=multi-center, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SA=single arm, SB=single blind, TB=triple blind, XO=crossover design
 Other abbreviations: ADHD=attention deficit hyperactivity disorder, ADHD-RS=ADHD rating scale, CGI-S=clinical global impression of severity, SF-36=36-item Short Form Health Survey, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham

Additional Evidence

Dose Simplification

A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '\$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
\$	\$0-\$30 per Rx
\$\$	\$31-\$50 per Rx
\$\$\$	\$51-\$100 per Rx
\$\$\$\$	\$101-\$200 per Rx
\$\$\$\$\$	Over \$200 per Rx

Rx=prescription

Table 9. Relative Cost of Dyanavel® XR

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amphetamine	extended-release suspension	Dyanavel® XR	\$\$\$	N/A

N/A=Not available

X. Conclusions

Dyanavel® XR (amphetamine) is a central nervous system stimulant indicated for the treatment of ADHD in patients six years and older. Dyanavel® XR uses a patented delivery system consisting of both immediate- and extended-release amphetamine and is the only once-daily, extended-release, amphetamine-based oral liquid approved to treat ADHD in children.³⁻⁶

Guidelines recommend the use of an agent approved by the Food and Drug Administration (FDA) for the initial pharmacologic treatment of ADHD and they do not give preference to one agent over another.⁷⁻¹⁰ The FDA-approval of Dyanavel XR® (amphetamine) was based on the results of a phase III randomized, placebo-controlled clinical trial in 108 children with ADHD aged six to 12 years. The first five weeks of the study were an open-label dose optimization period, with an initial dose of 2.5 mg or 5 mg daily, followed by a one-week, double-blind treatment period. The study met its primary endpoint of change in pre-dose Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-combined score, an ADHD functional assessment tool, at four hours post-dosing.

Secondary efficacy endpoints evaluated duration of onset and duration of action based on change in SKAMP-combined scores at 1, 2, 4, 6, 8, 10, 12 and 13 hours post-dose. The change in SKAMP-combined scores demonstrated a statistically significant improvement at all time points compared to placebo. These results are presented in the package insert.³ No additional clinical studies for Dyanavel XR® were identified.

There are several factors to take into consideration when selecting a pharmacologic agent for the treatment of children and adolescents with ADHD. This includes the presence of comorbid conditions, patient/family preference, storage/administration at school, history of substance abuse, drug diversion, pharmacokinetics, and adverse events.^{1,2} The advantage of a once-daily formulation is that the medication does not need to be taken during school hours, as is the case with the immediate-release formulations. Administration of medications during school hours, especially Schedule II controlled substances, can be difficult since the medication must be administered by a licensed school nurse.

There is insufficient evidence to support that one brand Dyanavel XR® (amphetamine) product is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand Dyanavel XR® (amphetamine) products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand amphetamine extended-release suspension product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.
2. Krull K. Attention deficit hyperactivity disorder in children and adolescents: Treatment with medications. In: UpToDate, Torchia, M (Ed), UpToDate, Waltham, MA, 2016 [cited 2016 Jan 26]. Available from: <http://www.utdol.com/utd/index.do>.
3. Dyanavel XR® [package insert]. Monmouth Junction (NJ): Tris Pharma, Inc.; 2017 Jan.
4. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2017 [cited 2017 Mar]. Available from: <http://www.thomsonhc.com/>.
5. Facts and Comparisons® eAnswers [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017 [cited Mar 2017]. Available from: <http://online.factsandcomparisons.com>.
6. Tris Pharma receives FDA approval of Dyanavel XR (amphetamine) CII as once-daily liquid for treatment of ADHD in Children [news release]. Monmouth Junction, NJ: Tris Pharma; October 20, 2015. Available from: <http://www.prnewswire.com/news-releases/tris-pharma-receives-fda-approval-of-dyanavel-xr-amphetamine-cii-as-once-daily-liquid-for-treatment-of-adhd-in-children-300162789.html>. Accessed March 2017.
7. American Academy of Pediatrics. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics*. 2011;128:1-16.
8. Institute for Clinical Systems Improvement. Health care guideline: diagnosis and management of attention deficit hyperactivity disorder in primary care for school-age children and adolescents [guideline on the Internet]. 9th ed. Bloomington (MN): Institute for Clinical Systems Improvement; March 2012. Available at: http://www.icsi.org/adhd/adhd_2300.html. Accessed January 2016.
9. National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people, and adults [guideline on the Internet]. London (UK). September 2008. Available at: <http://guidance.nice.org.uk/CG72>. Accessed January 2016.
10. Bolea-Alamañac B, Nutt DJ, Adamou M, et al. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2014. 1-25. DOI: 10.1177/0269881113519509.
11. McCracken JT, Biederman J, Greenhill LL et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLL381 (Adderall XR) in children with ADHD. *J Am Acad Child Adolesc Psychology*. 2003;426(6):673-83.
12. Pliszka SR, Browne RG, Olvera RL et al. A double-blind, placebo controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2000;39(5):619-26.
13. Pelham WE, Aronof HR, Midlam JL et al. A comparison of Ritalin and Adderall; efficacy and time course in children with attention hyperactivity deficit disorder. *Pediatrics*. 1999;103:e43.
14. Faraone SV, Biederman J, Roe C. Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. *J Clin Psychopharmacol*. 2002;22(5):468-73.
15. Biederman J, Lopez FA, Boellner SW, et al. A randomized, double blind, placebo controlled parallel group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2002;110:258-66.
16. Goodman DW, Ginsberg L, Weisler, RH, Cutler AJ, Hodgkins P. An Interim Analysis of the Quality of Life, Effectiveness, Safety, and Tolerability (Q.U.E.S.T.) Evaluation of Mixed Amphetamine Salts Extended Release in Adults With ADHD. *CNS Spectr*. 2005;10(Suppl 20):26-34.